ORIGINAL RESEARCH ARTICLE

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Effect of Exercise on Drug-Related Falls Among Persons with Alzheimer's Disease: A Secondary Analysis of the FINALEX Study

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Abstract

Introduction No study has investigated how exercise modifies the effect of fall-related drugs (FRDs) on falls among people with Alzheimer's disease (AD).

Objective The aim of this study was to investigate how exercise intervention and FRDs interact with fall risk among patients with AD.

Methods In the FINALEX trial, community-dwelling persons with AD received either home-based or group-based exercise twice weekly for 1 year ($n = 129$); the control group received normal care ($n = 65$). The number of falls was based on spouses' fall diaries. We examined the incidence rate ratios (IRRs) for falls among both non-users and users of various FRDs (antihypertensives, psychotropics, drugs with anticholinergic properties [DAPs]) in both control and combined intervention groups.

Results Between the intervention and control groups, there was no difference in the number of falls among those without antihypertensives or psychotropics. In the intervention group taking antihypertensives, the IRR was 0.5 falls/person-year (95% confidence interval [CI] 0.4–0.6), while in the control group, the IRR was 1.5 falls/person-year (95% CI 1.2–1.8) [$p < 0.001$ for group, $p = 0.067$ for medication, $p < 0.001$ for interaction]. Among patients using psychotropics, the intervention group had an IRR of 0.7 falls/person-year (95% CI 0.6–0.9), while the control group had an IRR of 2.0 falls/person-year (95% CI 1.6–2.5) [$p < 0.001$ for group, $p = 0.071$ for medication, $p < 0.001$ for interaction]. There was a significant difference in falls between the intervention and control groups not using DAPs (0.6, 95% CI 0.5–0.7; 1.2, 95% CI 1.0–1.4), and between the intervention and control groups using DAPs (1.1, 95% CI 0.8–1.3; 1.5, 95% CI 1.0–2.1) [$p < 0.001$ for group, $p = 0.014$ for medication, $p = 0.97$ for interaction].

Conclusion Exercise has the potential to decrease the risk for falls among people with AD using antihypertensives and psychotropics.

Trial Registration ACTRN12608000037303.

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Key Points

Exercise has the potential to reduce the fall risk related to antihypertensives and psychotropics among people with Alzheimer's disease (AD).

Exercise decreased the risk for falls regardless of polypharmacy among people with AD.

Drugs with anticholinergic properties (DAPs) increased the risk for falls; however, exercise reduced the risk among both non-users and users of DAPs among people with AD.

1 Introduction

Polypharmacy and several drug classes expose older people to the risk of falls [1]. The use of psychotropics is associated with falls among older people [2, 3], especially among nursing-home residents [4]. Furthermore, drugs with anticholinergic properties (DAPs) are associated with an increased frequency of falls [5, 6], while antihypertensives are associated with an increased risk for falls [2, 3] and hip fractures [7].

Approximately 60% of older persons with dementia or cognitive impairment fall annually [8, 9]. Several possible fall risk factors such as advanced age, female sex, history of falls, symptomatic orthostatic hypotension, disability, frailty, advanced dementia and comorbidities [10–18], as well as protective factors such as physical activity and better physical functioning [12, 18], have been suggested to be associated with falls among people with dementia. However, to our knowledge, fall-related drugs (FRDs) other than psychotropics have not been studied as risk factors among people with dementia.

Recent (2015) systematic reviews and meta-analyses found that physical exercise may significantly prevent falls, even among older persons with cognitive impairment [19] or dementia [20]. It has been suggested that the decrease in falls might be due to improvement in muscle strength and mobility functioning [15], although the exact mechanism remains unclear. Furthermore, no studies have examined whether exercise intervention can modify the risk of FRDs among persons with dementia.

The aim of this study, which is a secondary analysis of FINALEX trial data, was to investigate possible interactions between exercise intervention and FRDs on fall risk among patients with Alzheimer's disease (AD).

2 Methods

The FINALEX study investigated exercise among persons with AD [21]. The intervention participants experienced benefit with respect to falls [21], and we also found several risk and protective factors (including FRDs) for falls among patients with AD [18]. In the FINALEX study, patients with AD were comprehensively assessed at baseline for medication use and various other risk factors [21, 22]. In addition, patients' spouses kept detailed diaries on falls and their characteristics, during the follow-up year.

The original FINALEX study (a randomized controlled trial) had both home-based and group-based exercise intervention arms; the control group received normal community care [21]. The intervention groups fell significantly less during the 12 months of follow-up compared with the control group [21]. In this analysis, we merged the home-based and group-based intervention groups into a single intervention group, which we compared with the control group with regard to incidence rate ratios (IRRs) of falls, various FRDs, and their interaction.

2.1 Participants

In 2008, Alzheimer's patients living with a spouse in the cities of Helsinki, Vantaa or Espoo ($N = 1264$) were recruited by the Social Insurance Institution of Finland, based on its drug reimbursement register. An interest in participation was expressed by 497 persons, 390 of whom were able to be contacted by study nurses. Eighty-four persons did not wish to participate and 96 did not fulfil the inclusion criteria, which included the following: (1) Finnish-language speaker; (2) living with a spouse at home; (3) living in Helsinki, Vantaa or Espoo; (4) ≥ 65 years of age and retired; (5) absence of severe hemiplegia or diagnosed terminal disease; (6) able to walk independently with or without a mobility aid; and (7) having at least one sign of possible frailty (one or more falls during the previous year, unintentional weight loss, or decreased walking speed). A total of 210 patients met our inclusion criteria and were included and randomised in the study.

The study was approved by the Ethics Committee of the Helsinki University Hospital. Informed consent was obtained for all patients in the original FINALEX study, with spouses providing informed consent when the patients had reduced judgment capacity.

2.2 Clinical Measures

Demographic factors including sex, age, education and vision problems (reading ability) were recorded at baseline. Body mass index (BMI, the person's weight in kilograms divided by their height in meters squared) and blood pressure were also measured at baseline. The Mini Nutritional Assessment (MNA) [23] was used to assess the patient's nutritional status. Medical records confirmed medication use and comorbidities, after which the Charlson Comorbidity Index [24] was calculated. The Clinical Dementia Rating (CDR) scale [25] and the Mini-Mental State Examination (MMSE) [26] were used to evaluate cognitive status, whereas the Functional Independence Measure (FIM) [27] and Short Physical Performance Battery (SPPB) [28] were used to evaluate physical functioning and mobility. The SPPB includes tests of balance, walking speed, and rising from a chair; we administered the balance and walking speed tests separately [28]. The number of falls during a 12-month period was based on the fall diaries kept by the

patients' spouses during the study. At baseline, the spouses were asked if the patients had had fall(s) in the previous year.

Polypharmacy was defined as regularly taking nine or more systemic medications. In previous publications, polypharmacy has been defined as the use of five or more drugs, and excessive polypharmacy has been defined as more than nine drugs [29]. We used a cut-point of nine or more to increase the statistical power. Medications with World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) classification system codes [30] C03 (diuretics), C07 (beta-blocking agents), C08 (calcium channel blockers) and C09 (agents acting on the renin-angiotensin system) were included in antihypertensives, whereas medications with WHO ATC codes N05A (antipsychotics), N05B (anxiolytics), N05C (hypnotics and sedatives) and N06A (antidepressants) were included in psychotropics. DAPs were defined according to the Anticholinergic Risk Scale [31], and we also included B01AC07 (dipyridamole), R05DA04 (codeine) and N02AX02 (tramadol) from the Anticholinergic Drug Scale [32] as DAPs. Drug use was retrieved from medical records confirmed by spouses.

2.3 Interventions

A detailed description of the intervention has been previously published [22]. The health status of each patient starting in the intervention groups was assessed by a geriatrician to ensure patient safety.

The home exercise group received a tailored exercise intervention at patients' homes for two 1-h sessions weekly for 1 year. The intervention was administered by a physiotherapist and was individually tailored to improve everyday skills while taking into account patients' needs. The group-based exercise intervention group also trained for approximately 1 h twice weekly for 1 year. Adult daycare centre visits lasted for 4 h, of which the individual training time was approximately 1 h. Patients were transferred by taxis to daycare centres, and they also had lunch during the visits. The group consisted of 10 patients and two physiotherapists. Both groups performed aerobic, strength, balance, endurance and multitasking training.

The control group received normal community care and was allowed to receive rehabilitation in the public healthcare system, including physiotherapy.

All patients and their spousal caregivers in both the intervention and control groups received advice on nutrition and exercise. In addition, all patients were recommended to take vitamin D supplements (20 µg/day).

2.4 Statistical Analysis

The characteristics of the control and intervention groups are presented as means with standard deviations (SD), medians with interquartile ranges (IQRs), or as counts with percentages. Statistical comparison between the groups was performed by t test or bootstrap-type t-test; Chi square tests were performed when appropriate. Fall incidence rates (per person-year) with 95% confidence intervals (CIs) were calculated assuming a Poisson distribution. Poisson regression models with count of falls events as the main outcome were used to model the relationship between exercise and medication. Models included age, sex, and the motor part of the FIM test (FIMmotor) value as covariates. The assumptions of overdispersion in the Poisson model were tested using the Lagrange multiplier test, and the normality of the variables was tested using the Shapiro–Wilk W test. The Stata 15.0 statistical package (StataCorp LLC, College Station, TX, USA) was used for the analyses.

3 Results

Five patients died and 11 declined to participate immediately after randomization. Thus, a total of 194 patients were included in the analysis. The baseline characteristics are shown in Table 1 (the intervention and control groups); there were no significant differences in the baseline characteristics between these groups.

3.1 Incidence Rate Ratios of Falls Among Patients With or Without Various Fall-Related Drugs, Between the Intervention and Control Groups

Figure 1 shows the IRRs of falls during the 1-year trial. The four panels in Fig. 1 show falls among patients with or without polypharmacy, antihypertensives, psychotropics, or DAPs. The IRRs and 95% CIs are crude figures, whereas the p-values for group, medication and interaction are adjusted for sex, age, and FIMmotor (motor part of the FIM test).

Among those without polypharmacy, the intervention group had 0.6 falls per person-year (95% CI 0.5–0.8) and the control group had 1.0 falls per person-year (95% CI 0.8–1.3). Among those with polypharmacy, (nine or more regular drugs), the intervention group had 1.0 falls per person-year (95% CI 0.8–1.3) and the control group had 1.9 falls per person-year (95% CI 1.4–2.4) [$p < 0.001$ for group, $p = 0.23$ for medication, $p = 0.17$ for interaction, adjusted for sex, age, and FIMmotor].

Among those not taking antihypertensives, the intervention group had 1.2 falls per person-year (95% CI 1.0–1.4) and the control group had 0.9 falls per person-year (95% CI 0.6–1.2). Among those taking antihypertensives, the intervention group had 0.5 falls per person-year (95% CI 0.4–0.6) and the control group had 1.5 falls per person-year (95% CI 1.2–1.8)

Table 1 Baseline characteristics in the control and intervention groups

	Control (N=65)	Intervention (N=129)	p value[a]
Male [n (%)]	39 (60)	80 (62)	0.79
Age, years [mean (SD)]	78 (5)	78 (5)	0.75
Education < 8 years [n (%)]	29 (45)	48 (37)	0.32
BMI [mean (SD)]	25.0 (3.9)	25.9 (3.4)	0.12
MNA [mean (SD)]	22 (2)	23 (2)	0.29
Blood pressure [mean (SD)]			
Systolic	150 (27)	150 (25)	0.97
Diastolic	75 (12)	77 (12)	0.22
Charlson Comorbidity Index [24] [mean (SD)]	3.0 (1.7)	2.6 (1.8)	0.12
Number of drugs [mean (SD)]	6.6 (3.0)	6.5 (3.6)	0.94
CDR [n (%)]			0.72
0.5–1	22 (34)	44 (34)	
2	34 (52)	61 (47)	
3	9 (14)	24 (19)	
FIM [mean (SD)]	88 (18)	88 (19)	0.85
SPPB total [mean (SD)]	9.8 (2.0)	9.6 (2.3)	0.23
Vision problem [n (%)]	8 (12)	9 (7)	0.22
Fallen in previous year [n (%)]	32 (49)	48 (37)	0.11

[a]The difference between groups was tested by *t* test, bootstrap type *t* test, or Chi square test

SD standard deviation, *BMI* body mass index, *MNA* Mini-Nutritional Assessment [23], *CDR* Clinical Dementia Rating scale [25], *FIM* Functional Independence Measure [27], *SPPB* Short Physical Performance Battery [28]

[$p < 0.001$ for group, $p = 0.067$ for medication, $p < 0.001$ for interaction, adjusted for sex, age, and FIMmotor].

Among those not taking psychotropics, the intervention group had 0.7 falls per person-year (95% CI 0.6–0.9) and the control group had 0.8 falls per person-year (95% CI 0.6–1.0). Among those taking psychotropics, the intervention group had 0.7 falls per person-year (95% CI 0.6–0.9) and the control group had 2.0 falls per person-year (95% CI 1.6–2.5) [$p < 0.001$ for group, $p = 0.071$ for medication, $p < 0.001$ for interaction, adjusted for sex, age, and FIMmotor].

Among those not taking DAPs, the intervention group had 0.6 falls per person-year (95% CI 0.5–0.7) and the control group had 1.2 falls per person-year (95% CI 1.0–1.4). Among those taking DAPs, the intervention group had 1.1 falls per person-year (95% CI 0.8–1.3) and the control group had 1.5 falls per person-year (95% CI 1.0–2.1) [$p < 0.001$ for group, $p = 0.014$ for medication, $p = 0.97$ for interaction, adjusted for sex, age, and FIMmotor].

We performed additional analyses using age, sex, FIMmotor, Charlson Comorbidity Index and CDR class as covariates. These analyses did not change the main findings (data not shown).

4 Discussion

The exercise intervention significantly modified the risk for falls among patients using antihypertensive or psychotropic medications; however, the risk associated with taking DAPs or polypharmacy was not modified by exercise intervention. This is the first study to explore how exercise modifies the risk for falls caused by medications in patients with dementia.

A meta-analysis found exercise and multifactorial interventions to be most effective in reducing falls [33]. Other possible interventions for community-dwelling older persons include reducing the number of drugs, reducing psychoactive medications and modifying the home environment, as previously stated [1]. However, there are few studies that have investigated interventions to reduce falls among dementia patients. In 2015, two meta-analyses suggested that exercise has the potential to prevent falls among persons with known cognitive impairment and dementia [19, 20]; however, there is insufficient knowledge on the specific mechanisms on why and how
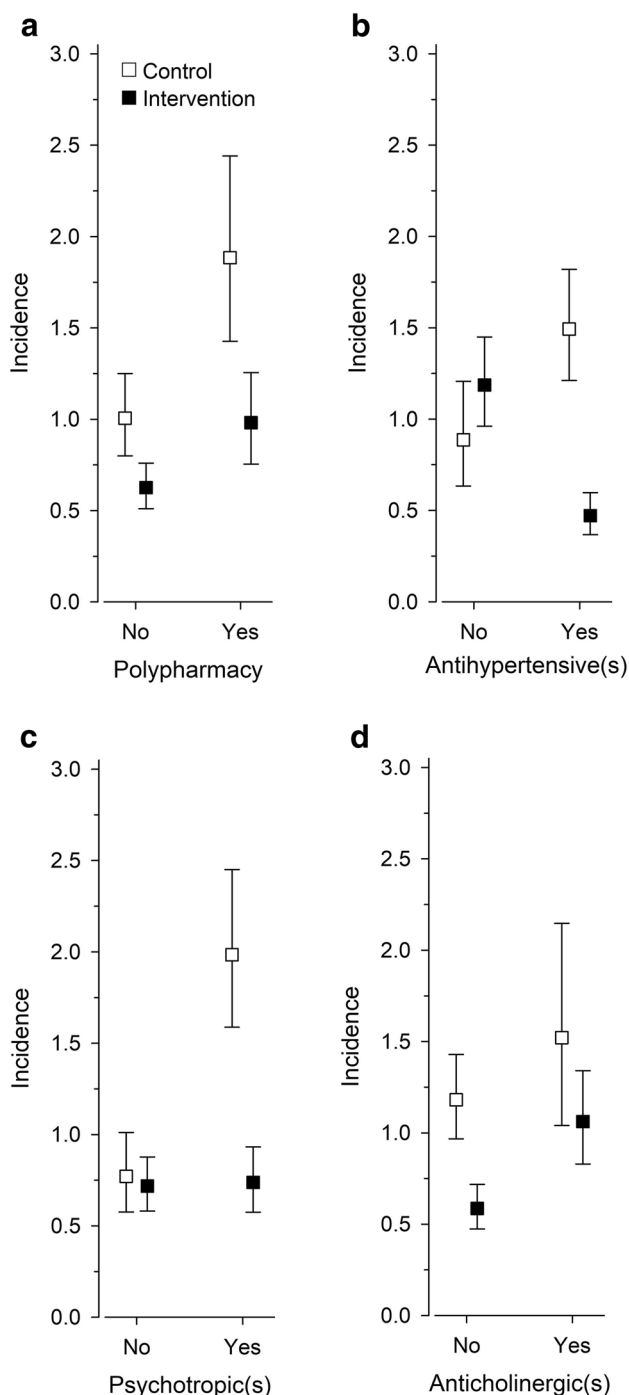
Fig. 1 Falls in participants with or without. **a** Polypharmacy, **b** antihypertensives, **c** psychotropics, and **d** DAPs. Values shown are incidence rate ratios ±95% confidence intervals. *DAPs* drugs with anticholinergic properties

exercise may reduce falls and whether there are interactions between risk and protective factors for falls. In this study, our purpose was to investigate possible interactions between exercise intervention and FRDs. The results from the present study add to the literature as we found exercise

intervention to interact with antihypertensives and psychotropics (Fig. 1). With respect to antihypertensives, the mechanism could be better circulation as exercise induces calf muscles to work better to enhance blood return to the heart and brain. In this way, exercise may decrease the risk related to some antihypertensives for orthostatic hypotension. For both medications, one explanation could be better balance and mobility as a result of exercise training. Although exercise intervention was associated with a reduced risk of falls among both DAP non-users and users, there was no interaction effect. A similar pattern was seen among those with and without polypharmacy.

While our findings indicate that these medications may increase the risk of falls among people with dementia, exercise has the potential to completely compensate for this risk among users of antihypertensives and psychotropics. Thus, dementia patients with hypertension should be encouraged to exercise. Exercise should also be encouraged among people with dementia taking psychotropics, although a reduction or deprescribing of psychotropics may be the primary aim to decrease the risk of falls. Exercise should also be encouraged among people with dementia with polypharmacy or taking DAPs. However, exercise does not completely compensate for their risk of falls, thus the primary aim for these patients should be to reduce polypharmacy and deprescribe DAPs.

The FINALEX study (a randomized controlled trial) has several strengths. Every participant had a confirmed diagnosis of AD. The intervention was highly coordinated and a physiotherapist supervised each training session. The intervention was also frequent (twice weekly) and long term (12 months). The intervention (implemented by physiotherapists in primary care) did not increase the total costs of social and health services [21]. Fall diaries kept by spouses served to assess the falls (a diary is a highly sensitive method to accurately record falls) [34]. The medications used were confirmed from both medical records and spousal caregivers. There were no significant differences in the baseline characteristics between the intervention and control groups. In addition, the baseline characteristics presented similar features as seen in previous studies among dementia patients [12], giving reliability to the results in this patient group.

This study also has several limitations. All participants were community-dwelling Caucasians living in their homes with their spousal caregivers. Generalising these results to other populations should be undertaken with caution. An ideal design to test our hypothesis would be randomizing AD patients taking psychotropics or antihypertensives into two groups and testing exercise intervention among these groups; however, recruitment into this kind of trial might be challenging. This is a subgroup analysis of the original randomised trial and we combined the original two intervention groups. The small sample size decreased the power of the study and the study was

not blinded; however, the study nurses collecting the data were uninformed about the exact intervention and primary outcome measures and were not researchers in the study. Moreover, the spousal caregivers' evaluations were used to assess the FIM scores [27] and falls of the patients. Spouses were also not aware of the study hypothesis. The differences between the original intervention and control groups were probably decreased because patients in the control group received high-quality community care and were also allowed to receive physiotherapy. Although medications used at the end of the study were not confirmed, this study intervention did not intend to change them.

5 Conclusions

The exercise intervention in the FINALEX study has the potential to modify the risk of falls among people with dementia taking antihypertensives and psychotropics. Exercise is beneficial to all people with dementia; however, primary care should pay particular attention to people with dementia taking antihypertensives or psychotropics for medical conditions, and motivate them to exercise to reduce their risk of falls.

Compliance with Ethical Standards

Conflicts of interest Niko Perttila, Hanna Öhman, Timo Strandberg, Hannu Kautiainen, Minna Raivio, Marja-Liisa Laakkonen, Niina Savikko, Reijo Tilvis and Kaisu Pitkälä declare that they have no conflicts of interest relevant to the content of this review. The authors are independent researchers who have no association with the sponsors.

Ethical approval All procedures performed in the original FINALEX study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The original FINALEX study and this subgroup analysis of that study were approved by the Ethics Committee of the Helsinki University Hospital.

Informed consent Informed consent was obtained for all patients in the original FINALEX study. Spouses provided informed consent when patients had reduced judgment capacity.

References

1. 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(1):148–57.
2. Hartikainen S, Lonnroos E, Louhivuori K. Medication as a risk factor for falls: critical systematic review. J Gerontol A Biol Sci Med Sci. 2007;62(10):1172–81.
3. Woolcott JC, Richardson KJ, Wiens MO, et al. Meta-analysis of the impact of 9 medication classes on falls in elderly persons. Arch Intern Med. 2009;169(21):1952–60.
4. Lapeyre-Mestre M. A review of adverse outcomes associated with psychoactive drug use in nursing home residents with dementia. Drugs Aging. 2016;33(12):865–88.
5. Cardwell K, Hughes CM, Ryan C. The association between anticholinergic medication burden and health related outcomes in the 'oldest old': a systematic review of the literature. Drugs Aging. 2015;32(10):835–48.
6. Mayer T, Meid AD, Saum KU, et al. Comparison of nine instruments to calculate anticholinergic load in a large cohort of older outpatients: association with cognitive and functional decline, falls, and use of laxatives. Am J Geriatr Psychiatry. 2017;25(5):531–40.
7. Corrao G, Mazzola P, Monzio Compagnoni M, et al. Antihypertensive medications, loop diuretics, and risk of hip fracture in the elderly: a population-based cohort study of 81,617 Italian patients newly treated between 2005 and 2009. Drugs Aging. 2015;32(11):927–36.
8. Tinetti ME, Speechley M, Ginter SF. Risk factors for falls among elderly persons living in the community. N Engl J Med. 1988;319(26):1701–7.
9. van Dijk PT, Meulenberg OG, van de Sande HJ, Habbema JD. Falls in dementia patients. Gerontologist. 1993;33(2):200–4.
10. Salva A, Roque M, Rojano X, et al. Falls and risk factors for falls in community-dwelling adults with dementia (NutriAlz trial). Alzheimer Dis Assoc Disord. 2012;26(1):74–80.
11. Meuleners LB, Fraser ML, Bulsara MK, Chow K, Ng JQ. Risk factors for recurrent injurious falls that require hospitalization for older adults with dementia: a population based study. BMC Neurol. 2016;16(1):188.
12. Allan LM, Ballard CG, Rowan EN, Kenny RA. Incidence and prediction of falls in dementia: a prospective study in older people. PLoS One. 2009;4(5):e5521.
13. Perttila NM, Öhman H, Strandberg TE, et al. Severity of frailty and the outcome of exercise intervention among participants with Alzheimer disease: a sub-group analysis of a randomized controlled trial. Eur Geriatr Med. 2016;7(2):117–21.
14. Gleason CE, Gangnon RE, Fischer BL, Mahoney JE. Increased risk for falling associated with subtle cognitive impairment: secondary analysis of a randomized clinical trial. Dement Geriatr Cogn Disord. 2009;27(6):557–63.
15. Ohman H, Savikko N, Strandberg T, et al. Effects of exercise on functional performance and fall rate in subjects with mild or advanced Alzheimer's disease: secondary analyses of a randomized controlled study. Dement Geriatr Cogn Disord. 2016;41(3–4):233–41.

16. Kudo Y, Imamura T, Sato A, Endo N. Risk factors for falls in community-dwelling patients with Alzheimer's disease and dementia with Lewy bodies: walking with visuocognitive impairment may cause a fall. Dement Geriatr Cogn Disord. 2009;27(2):139–46.

17. Horikawa E, Matsui T, Arai H, Seki T, Iwasaki K, Sasaki H. Risk of falls in Alzheimer's disease: a prospective study. Intern Med. 2005;44(7):717–21.

18. Perttila NM, Ohman H, Strandberg TE, et al. How do community-dwelling persons with Alzheimer disease fall? Falls in the FINA-LEX study. Dement Geriatr Cogn Dis Extra. 2017;7(2):195–203.

19. Chan WC, Yeung JW, Wong CS, et al. Efficacy of physical exercise in preventing falls in older adults with cognitive impairment: a systematic review and meta-analysis. J Am Med Dir Assoc. 2015;16(2):149–54.

20. Burton E, Cavalheri V, Adams R, et al. Effectiveness of exercise programs to reduce falls in older people with dementia living in the community: a systematic review and meta-analysis. Clin Interv Aging. 2015;10:421–34.

21. Pitkala KH, Poysti MM, Laakkonen ML, et al. Effects of the Finnish Alzheimer disease exercise trial (FINALEX): a randomized controlled trial. JAMA Intern Med. 2013;173(10):894–901.

22. Pitkala KH, Raivio MM, Laakkonen ML, Tilvis RS, Kautiainen H, Strandberg TE. Exercise rehabilitation on home-dwelling patients with Alzheimer's disease–a randomized, controlled trial. Study Protocol. 2010;11:92.

23. Guigoz Y, Lauque S, Vellas BJ. Identifying the elderly at risk for malnutrition. The Mini Nutritional Assessment. Clin Geriatr Med. 2002;18(4):737–57.

24. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373–83.

25. Hughes CP, Berg L, Danziger WL, Coben LA, Martin RL. A new clinical scale for the staging of dementia. Br J Psychiatry. 1982;140:566–72.

26. 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(3):189–98.

27. Pollak N, Rheault W, Stoecker JL. Reliability and validity of the FIM for persons aged 80 years and above from a multilevel continuing care retirement community. Arch Phys Med Rehabil. 1996;77(10):1056–61.

28. Guralnik JM, Simonsick EM, Ferrucci L, et al. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. J Gerontol. 1994;49(2):M85–94.

29. Onder G, Liperoti R, Fialova D, et al. Polypharmacy in nursing home in Europe: results from the SHELTER study. J Gerontol A Biol Sci Med Sci. 2012;67(6):698–704.

30. WHO. WHO Collaborating Centre for Drug Statistics Methodology. 2017. Available at: https://www.whocc.no/atc_ddd_index/. Accessed 1 Apr 2018.

31. Rudolph JL, Salow MJ, Angelini MC, McGlinchey RE. The anticholinergic risk scale and anticholinergic adverse effects in older persons. Arch Intern Med. 2008;168(5):508–13.

32. Carnahan RM, Lund BC, Perry PJ, Pollock BG, Culp KR. The Anticholinergic Drug Scale as a measure of drug-related anticholinergic burden: associations with serum anticholinergic activity. J Clin Pharmacol. 2006;46(12):1481–6.

33. Chang JT, Morton SC, Rubenstein LZ, et al. Interventions for the prevention of falls in older adults: systematic review and meta-analysis of randomised clinical trials. BMJ. 2004;328(7441):680.

34. Hannan MT, Gagnon MM, Aneja J, et al. Optimizing the tracking of falls in studies of older participants: comparison of quarterly telephone recall with monthly falls calendars in the MOBILIZE Boston Study. Am J Epidemiol. 2010;171(9):1031–6.