The effect of multidomain lifestyle intervention on daily functioning in older people

Suggested running title: Lifestyle intervention and daily functioning

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Word count (text): 3113
Word count (abstract): 271

ACKNOWLEDGEMENTS

Disclosures: Kulmala, Havulinna, Ngandu, Levälahti, Lehtisalo, Peltonen, Pippola, Solomon report no disclosures. Dr. Kivipelto has served on scientific advisory boards for Pfizer Inc. and Elan Corporation; served on the editorial advisory board of the Journal of Alzheimer's Disease and has received speaker honoraria from Janssen, Novartis, and Pfizer Inc. Dr. Strandberg has made various cooperation (research, consultative, educational) with several companies marketing cardiovascular drugs. Dr Soininen has served in advisory boards of ACImmine and Merck.

Declaration of sources of funding: FINGER study is financially supported by Academy of Finland's Responding to Public Health Challenges Research Programme (SALVE) and Academy of Finland grants 278457, 317465 (MK), 287490, 294061, and 319318 (AS), Academy of Finland Key Project Funding 305810 (Muistikko), European Research Council 804371 (AS), La Carita Foundation, Juho Vainio Foundation, Finnish Medical Foundation (TN), Finnish Social Insurance Institution, Ministry of Education and Culture Research Grant (MK, JK), EVO/VTR grants of University Hospitals of Kuopio, Oulu and Turku, Seinäjoki Central hospital and Oulu City Hospital, Yrjö Jahnsson Foundation, Finnish Cultural Foundation, South Ostrobothnia Regional fund, Swedish Research Council, Alzheimerfonden, Stockholm County Council (ALF), Alzheimer's Research & Prevention Foundation USA, AXA Research Fund, Knut and Alice Wallenberg Foundation Sweden, Center for Innovative Medicine (CIMED) at Karolinska Institutet Sweden, Stiftelsen Stockholms sjukhem Sweden, Konung Gustaf V:s och Drottning Victorias Frimurarstiftelse Sweden.

IMPACT STATEMENT

We certify that this work is novel clinical research. The current study is among the first trials showing the effects of a multifactorial lifestyle intervention on the daily functioning of community-dwelling older persons who are at-risk of cognitive decline. The results showed that a healthy lifestyle may promote functional independence in the at-risk older population.

ABSTRACT

Objectives: To investigate the effect of a 2-year multidomain lifestyle intervention on daily functioning of older people.

Design: 2-year randomized-controlled trial (ClinicalTrials.gov, NCT01041989).

Setting: Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER)

Participants: 1,260 older adults, with a mean age 69 years at the baseline who were at risk of cognitive decline.

Intervention: A multidomain intervention including simultaneous physical activity intervention, nutritional counselling, vascular risk monitoring and management, and cognitive training and social activity.

Measurements: The ability to perform daily activities (ADL, IADL) and physical performance (SPPB).

Results: The mean baseline ADL score was 18.1 (SD 2.6) points; scale ranging from 17 (no difficulties) to 85 (total ADL dependence). During the 2-year intervention, the ADL disability score slightly increased in the control group, while in the intervention group it remained relatively stable. Based on the latent growth curve model, the difference in the change between the intervention and control groups was -0.95 (95% CI -1.61 to -0.28) after one year and -1.20 (95% CI -2.02 to -0.38) after two years. In terms of physical performance, the intervention group had a slightly higher probability of improvement (from score 3 to score 4, p=0.041) and a lower probability of decline (from score 3 to scores 0-2, p=0.043) for chair rise compared to the control group.

Conclusion: A 2-year lifestyle intervention was able to maintain the daily functioning of the at-risk older population. The clinical significance of these results in this fairly well-functioning population remains uncertain, but the study results hold promise that healthy eating, exercise and cognitive and social activity may have favourable effects on functional independence in old age.

Key words: clinical trial, disablement process, functional performance, preventative health care

INTRODUCTION

Adequate ability to perform daily tasks and physical performance are prerequisites for independent living. Disability refers to difficulties or the inability to perform basic activities of daily living (BADL), such as bathing, dressing, transferring into a bed[1]or more demanding instrumental activities of daily living (IADL), such as coping with housework, handling finances or using a telephone[2]. The disablement model by Verbrugge & Jette (1994) demonstrates how functional limitations usually precede disability in BADLs and IADLs[3]. Functional decline and disability increase the risk of several adverse health events, including injuries[4], hospital care and premature death[5].

Lifestyle-related risk factors for disability have been relatively widely reported. Longitudinal studies have reported that physically inactive persons reach the disability threshold level earlier[6]. A healthy diet and avoiding obesity are also associated with lower risk of functional decline in old age[7] and several chronic conditions, including high blood pressure and cardiovascular diseases may accelerate the decline[8]. However, only a few large randomized controlled trials (RCT) have investigated whether simultaneous changes in diet, increasing physical exercise or

modifying cardiovascular risks slow down the progression or prevent BADL/IADL disabilities. A few recent intervention studies with different designs have not produced uniform results[9-10]. This study reports findings from the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER), which is the first large RCT targeting persons at risk of cognitive decline with a multidomain intervention including simultaneous physical activity, nutritional counselling, vascular risk monitoring and management, and cognitive training and social activity[11,12]. The FINGER study has demonstrated significant intervention effects on the primary outcome (overall cognition) and main cognitive secondary outcomes (executive functioning and processing speed). Most secondary outcomes[12] of the FINGER study have already been reported[13-15]. For health resources, biomarkers and mortality analyses are ongoing. In the current study we evaluated whether a multidomain lifestyle intervention reduces a decline in physical performance measured by testing standing balance, a timed sit-to stand and 4 meters comfortable walking time[12]. We also conducted exploratory analyses investigating the intervention effects on disability measured with a self-reported assessment of the ability to perform daily living activities.

MATERIALS AND METHODS

Participants

FINGER (ClinicalTrials.gov identifier: NCT01041989)[11-13] includes altogether 1,260 independently living older persons from six cities in Finland. The full FINGER study protocol, recruitment of the participants, baseline characteristics and outcomes have been reported in detail previously[11,12]. The inclusion criteria were that the participants were at an age of 60–77 years at the start of the study, had a CAIDE (Cardiovascular Risk Factors, Aging and Dementia)

Dementia Risk Score[16] of 6 points or higher and a cognitive performance at the mean level or slightly lower than expected for their age according to Finnish population norms tested with the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropsychological battery[17]. Persons with previously diagnosed or suspected dementia, disorders affecting safe engagement in the intervention (e.g. malignant disease, major depression, symptomatic cardiovascular disease, revascularization within 1 year previously), severe loss of vision, hearing, or communicative ability, disorders preventing cooperation as judged by the study physician were excluded.

FINGER intervention

Participants were randomly assigned into groups receiving intensive multidomain intervention or regular health advice (control group) at a 1:1 ratio. Computer-generated allocation was carried out in blocks of four (two individuals randomly allocated to each group) at each site after the baseline by the study nurse. The group allocation was not actively explained to the participants. The intervention components have been described in detail previously[11,12]. Briefly, the multidomain intervention included simultaneous physical activity intervention, nutritional counselling, vascular risk monitoring and management, and cognitive training and social activity. The nutritional component was based on the Finnish Nutrition Recommendations[18] and was conducted by study nutritionists (three individual sessions and seven to nine group sessions). The physical activity component was based on international guidelines[19] and a modified version of the Dose Responses to Exercise Training (DR's EXTRA) study protocol[20]. Training was guided by physiotherapists at a gym and consisted of individually tailored programs for progressive muscle strength training (1–3 times per week) and aerobic exercise (2–5 times per week). Exercises improving postural balance

were also included. Cognitive training included ten group sessions led by a psychologist. Individual sessions consisted of independent computer-based training at home or at the study site. Two six month periods included 72 training sessions each (three times per week, 10–15 min per session). The training programme was a web-based in-house developed computer program, which included several cognitive tasks adapted from previous randomized controlled trials[21]. Social activities were stimulated through the numerous group meetings. The management of metabolic and vascular risk factors was based on national evidence-based guidelines[22-24]. Blood pressure, weight, BMI, and hip and waist circumference were regularly examined, and the participants received advice on leading a healthy lifestyle. Adherence was the highest for cardiovascular monitoring and individual nutritional counselling, intermediate for cognitive training and nutrition group visits and lower for independent gym training and computerized computer training (more detailed adherence data is presented in Supplementary Table S1).

The FINGER study was approved by the coordinating ethics committee of the Hospital District of Helsinki and Uusimaa. The participants gave their informed written consent prior to the study. The FINGER trial is registered with ClinicalTrials.gov, number NCT01041989.

Outcome measures

Activities of daily living disability

Basic activities of daily living (BADL) and instrumental activities of daily living (IADL) were assessed using questionnaires[1,2,25] . Hereafter in the text we use the term ADL to refer to the questionnaire covering both BADL and IADL components. The questionnaire included seventeen items. The ability to perform the following daily activities were assessed: toileting, eating, bathing, moving to and out of bed, dressing, moving indoors, walking up and down stairs,

cutting toe nails, taking and handling medications, using a telephone, cooking, light housework, handling finances, doing laundry, using public transportation, shopping and heavy housework. The response options were 1) able to independently perform the activity without any difficulties, 2) able to independently perform the activity, but with minor difficulties, 3) able to independently perform the activity, but with major difficulties, 4) able to perform the activity only when assisted, 5) not able to perform the activity even when assisted. A sum score based on the ADL questions (range 17-85), at the baseline, 12-month follow-up and 24-month follow up was calculated. Higher score indicated poorer daily functioning and score 17 no problems in any task.

Physical performance

The Short Physical Performance Battery (SPPB)[26] was administered to all participants before and after the intervention period. The SPPB consists of three subtests: a hierarchical test of balance, a four-meter walk at a normal pace and standing up from a chair five times consecutively. In the balance test, the participants were asked to remain standing with their feet as close together as possible, then in a semi-tandem position, i.e. with heel of one foot alongside the big toe of the other foot, and finally in a tandem position, i.e. with heel of one foot directly in front of the other foot and touching it. Each position had to be held for 10 seconds. For gait speed, the time required to walk 4 meters at a normal pace was measured. This test was repeated twice and the better time of the two was used in the analyses. For the chair rise test, participants were asked to stand up and sit down in a chair five times as quickly as they could with their arms crossed over the chest and the time required was measured. Each test was scored from 0 (worst performance) to 4 (best performance). We have previously reported analyses with the continuous SPPB sum

score as an outcome. The intervention and control groups did not differ significantly, but the estimate (95% CI) was 0.03 (-0.04-0.10) in favor of intervention[13]. The present analyses were done to investigate the intervention effects on the chair rise, balance and walking ability, because the intervention may have different effects on these tasks, which vary in difficulty.

Statistical analyses

We applied a latent-growth curve modeling approach for the ADL using all three time points (baseline, 12 months and 24 months) to analyze the change during 24 months. To account for a non-normal distribution of the ADL, a censored normal model was assumed with a minimum ADL score (17) as censoring point (i.e. floor effect). Change was assumed to be nonlinear by estimating the shape parameter (i.e. factor loading for a 12-month score) of the growth factor as free as opposed to a linear change model where the shape parameter is fixed. Mplus version 5.1 was used with full information maximum likelihood (FIML) estimation. FIML uses all available data by assuming that missing data is random. Because of the censored normal model, the integration algorithm was applied.

For ordinal scale SPPB scores, an ordered logistic regression model was applied. For analyses, participants with scores 0-2 in each domain were combined due to the limited number of persons in these categories. A 24-month score was the model outcome, while the baseline score, group and baseline score-group -interaction were the covariates. Based on an ordered logistic regression model, conditional transitions by model covariate categories were estimated with 95% confidence intervals and differences between groups were tested. An omnibus p-value for all

transitions was calculated by testing the joint hypotheses (Stata's test command applying accumulate option).

Additional analyses using logistic regression including only the persons without any difficulties in the ADLs (total score 17, n=774) at the baseline and persons without any difficulties in the SPPB (total score of 12, n=460) at the baseline were conducted to investigate the risk for ADL and SPPB incident difficulties in the intervention and control groups.

RESULTS

Population characteristics

At the baseline, the participants' ages ranged from 60-77 years (mean 69 years). The mean MMSE score at the baseline was 26.7 points, the mean BMI 28.2, and the mean education level was 10 years. A total of 71% were physically active at least twice a week. The baseline characteristics for the participants in the intervention and control groups are presented in Table 1. The flowchart shows the the number of participants assessed for eligibility and the flow of participants (Figure 1).

The ADL sum score in FINGER participants ranged from 17 to 46 at the baseline, from 17 to 51 at the 12-month follow-up and from 17 to 59 at the 24-month follow-up. In comparison, the full range of the ADL scale was 17 (no difficulties) to 85 (total ADL dependence). The mean ADL total score at the baseline was 18.1 (SD 2.6) points and the mean SPPB score was 10.8 (12 points indicating no difficulties). Table 2 shows the mean ADL and SPPB scores at the baseline and the mean change over time. The number of persons with difficulties in ADL and functional performance are presented in Supplementary Table S2.

Results from the latent-growth curve modelling showed that the ADL disability score slightly increased in the control group (the 12-month estimated mean change was 0.88, 95% CI 0.34 to 1.42; and for 24 months it was 1.10, 95% CI 0.53 to 1.67), while in the intervention group it remained stable (the 12 month estimated mean change was -0.12, 95% CI -0.61 to 0.38; and for 24 months it was -0.15, 95% CI -0.77 to 0.48). The difference in the change between the intervention and control groups was -0.95 (95% CI -1.61 to -0.28) after one year and -1.20 (95% CI -2.02 to -0.38) in two years indicating increased disability in the control group compared to the intervention group (Figure 2). The effect size (Cohen's d) and the 95% confidence interval for ADL was -0.31 (-0.53 to -0.09) after one year and -0.39 (-0.66 to -0.12) after two years.

The FINGER participants displayed good physical performance and it remained relatively stable over two years. Distributions of the SPPB scores at baseline and at the 2-year follow-up are shown in Supplementary Table S3. A total of 227 participants improved (30%) and 308 declined (22%) in their total SPPB scores over the two years, with a mean improvement of 1.5 (SD 0.9) points, and a mean decline of -1.2 (SD 0.5) points. Significant differences in the transitions between the groups were observed only for the chair rise test, where the intervention group had a slightly higher probability of improving and a lower probability of decline compared to the control group. All the transitions in the chair rise, balance and walking test according to the baseline score and group, and differences between the intervention and control group (percent with 95% confidence intervals) are shown in Supplementary tables S4-S6.

The risk of incident ADL disability among those without any baseline difficulties during the 2-year intervention period was significantly lower in the intervention group (OR 0.57, 95%CI 0.39 to 0.84). Intervention was not associated with incident limitations in physical performance (OR 1.29, 95% CI 0.84 to 2.00).

DISCUSSION

This study showed that 2-year multidomain intervention could maintain daily functioning of older people who are at risk of cognitive decline. The ADL disability score slightly increased in the control group during the intervention, while in the intervention group it remained stable. Intervention had also small favorable effects on chair rise. The clinical significance of these findings observed in a fairly well-functioning population remains uncertain. Although statistically significant, the observed changes in ADL score were small during the short within-study follow-up period of 2-years. The trial was powered to demonstrate the effectiveness of the intervention and the true potential of the intervention will become clear after longer follow-up time. Still, this beneficial effect on activities of daily living after 2 years in older population who are at risk for cognitive decline may be relevant for public health.

The current study is among the first trials showing the effects of a multifactorial lifestyle intervention on the daily functioning and physical performance of community-dwelling older people who are at risk of cognitive decline. Maintaining or improving physical functioning and detecting the first signs of functional decline at the ages of 65-80 may have far-reaching implications for improving functional independence after the age of 80[27]. In most countries, the

oldest old are now the fastest growing part of the overall population and it is essential to find ways to promote their healthy and independent living. The multidomain intervention was associated with lower odds of incident ADL disabilities. This may have clinical significance, since it has been previously shown that moving from being robust to physically frail within a few-years' time significantly increases the mortality risk[28]. Our findings are supported by the cohort study showing that better walking ability and a better-quality diet were significantly associated with a compression of the disabled period[29].

In our study of a population with a mean age of 69 years, 36% had at least some difficulties in daily activities at the baseline and 62% had at least some difficulties in physical performance. However, the mean ADL total score at the baseline was 18 points (17 points indicating no difficulties in ADLs) and a mean SPPB score of 11 (12 points indicating no difficulties), which indicated that the participants in the FINGER study were healthy and functionally independent. Previous studies have shown that the ADL/IADL disability ranges between 2-20%[30-32] among older people aged 60 to 80 years depending on the age group and ADL disability definition used. Thus, our sample can be considered representative of the population at this age. Changes in outcomes during the two-year intervention in this well-functioning population were relatively small. In single-domain intervention studies with similar outcomes, larger changes have been observed, however the study populations have been older and with more functional limitations at the baseline[33-34].

A few study limitations must be considered. Due to relatively well-functioning study population, there was only a little room for improvement in physical functioning during the 2-year period

and the outcome measures used may have suffered from a ceiling effect. The currently ongoing FINGER 7-year follow-up phase will provide more information on the longer-term effects of the intervention as the individuals get older and most likely develop more impairments. The aim of the FINGER intervention was to target an at-risk population and to start very early before cognitive or functional decline has started. Therefore it is not easy to see the intervention effects after 2 years. However, by starting early we will most likely achieve better long term effects. Also due to the small number of participants in some of the categories in the functional performance tests, the lack of statistical power in some of the analyses may limit the findings. Although the subgroup analyses showed that the intervention prevented incident ADL limitations, these results should be interpreted with caution because the changes were small, and the two groups were slightly different at the baseline and adjusting for the baseline level may not correct this completely. It should also be noted that the main outcome of the FINGER study was cognition and the multidomain intervention was not specifically planned for improving daily functioning.

Due to the multidomain approach, it is not possible to exactly state the individual effects of different intervention components on the observed effects. For similar outcomes, previous studies with physical activity interventions have provided beneficial effects on physical functioning[35,36] and therefore it is likely that intensive physical activity training is one of the key components of the FINGER program. In future studies, the FINGER-type multimodal intervention model needs to be investigated further, particularly with regard to the contribution of each component to the overall effect.

The strengths of this study include the controlled randomized study design with a large sample size, longer duration than in most trials, detailed outcome assessments and high-quality data collection. The multidomain lifestyle intervention was found to be feasible and safe with no serious adverse events[13]. Also the dropout rate was very low (12%). We used validated performance-based outcome measures of physical performance and the widely used scale of ADL functions. This study provides a reference frame for changes in daily functioning for older people who are at risk of dementia but have not yet developed significant impairments.

Independent daily functioning and physical performance in old age are influenced by a wide range of health- and lifestyle-related factors. A multidomain intervention simultaneously targeting multiple risk factors may prevent ADL disabilities in the older at-risk population. The FINGER study has shown that modifying older at-risk people's lifestyles has beneficial effects on cognition[13], and the quality of life[14], and as shown in the present study also on daily functioning. This study together with future multidomain intervention studies following the protocol of the FINGER study will provide additional understanding on the benefits of multidomain lifestyle interventions on the prevention of disability among old people at-risk of cognitive decline.

ACKNOWLEDGEMENTS

Conflict of Interest: There are no conflicts of interest.

Author's Contributions: TN, AS, RA, TL, MP, RR, TS, JT, HS, and MK conceived and designed the trial. TN, JLe and MK coordinated the trial. JLe (nutrition), RR, SH (physical exercise), TN (cognitive training), TS, RA and JT (vascular risk monitoring) designed and

supervised intervention components. JK, TN, JLe and EL did the data analysis. JK, TN, JLe and EL interpreted the results and drafted the report. JK, TN, AS, RA, TL, MP, RR, TS, JT, HS, and MK obtained funding. All authors revised the article for important intellectual content.

Sponsor's role: The funding sources had no role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript.

Acknowledgements: We thank all members of the FINGER study group for their cooperation in data collection and management. We are indebted to all the participants for their commitment to the study.

REFERENCES

1. Katz S, Ford AB, Moskowitz RW, Jackson BA, Jaffe MW. Studies of illness in the aged. The index of ADL: A standardized measure of biological and psychosocial function. *JAMA*. 1963;185:914-919.

2. Lawton MP, Brody EM. Assessment of older people: Self-maintaining and instrumental activities of daily living. *Gerontologist*. 1969;9(3):179-186.

3. Verbrugge LM, Jette AM. The disablement process. *Soc Sci Med*. 1994;38(1):1-14.

4. Ambrose AF, Paul G, Hausdorff JM. Risk factors for falls among older adults: A review of the literature. *Maturitas*. 2013;75(1):51-61.

5. Hardy SE, Kang Y, Studenski SA, Degenholtz HB. Ability to walk 1/4 mile predicts subsequent disability, mortality, and health care costs. *J Gen Intern Med*. 2011;26(2):130-135.

6. May AM, Struijk EA, Fransen HP, et al. The impact of a healthy lifestyle on disability-adjusted life years: A prospective cohort study. *BMC Med*. 2015;13:39-015-0287-6.

7. Backholer K, Pasupathi K, Wong E, Hodge A, Stevenson C, Peeters A. The relationship between body mass index prior to old age and disability in old age. *Int J Obes (Lond)*. 2012;36(9):1180-1186.

8. Bouillon K, Batty GD, Hamer M, et al. Cardiovascular disease risk scores in identifying future frailty: The Whitehall II prospective cohort study. *Heart*. 2013;99(10):737-742.

9. Houston DK, Leng X, Bray GA, et al. A long-term intensive lifestyle intervention and physical function: The look AHEAD movement and memory study. *Obesity (Silver Spring)*. 2015;23(1):77-84.

10. Ball K, Berch DB, Helmers KF, et al. Effects of cognitive training interventions with older adults: A randomized controlled trial. *JAMA*. 2002;288(18):2271-2281.

11. Ngandu T, Lehtisalo J, Levalahti E, et al. Recruitment and baseline characteristics of participants in the Finnish geriatric intervention study to prevent cognitive impairment and disability (FINGER)-A randomized controlled lifestyle trial. *Int J Environ Res Public Health*. 2014;11(9):9345-9360.

12. Kivipelto M, Solomon A, Ahtiluoto S, et al. The Finnish geriatric intervention study to prevent cognitive impairment and disability (FINGER): Study design and progress. *Alzheimers Dement*. 2013; 9(6):657-65.

13. Ngandu T, Lehtisalo J, Solomon A, et al. A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): A randomised controlled trial. *Lancet*. 2015;385(9984):2255-2263.

14. T.E. Strandberg E. Levalahti, T. Ngandu A. Solomon, M. Kivipelto for the FINGER Study Group. Health-related quality of life in a multidomain intervention trial to prevent cognitive decline (FINGER) *European Geriatric Medicine 8 (2017) 164–167*.

15. Marengoni A, Rizzuto D, Fratiglioni L, et al. The Effect of a 2-Year Intervention Consisting of Diet, Physical Exercise, Cognitive Training, and Monitoring of Vascular Risk on Chronic Morbidity-the FINGER Randomized Controlled Trial. *J Am Med Dir Assoc.* 2018 Apr;19(4):355-360.e1.

16. Kivipelto M, Ngandu T, Laatikainen T, Winblad B, Soininen H, Tuomilehto J. Risk score for the prediction of dementia risk in 20 years among middle aged people: A longitudinal, population-based study. *Lancet Neurol*. 2006;5(9):735-741.

17. Morris JC, Heyman A, Mohs RC, et al. The consortium to establish a registry for Alzheimer's disease (CERAD). Part I. Clinical and neuropsychological assessment of Alzheimer's disease. *Neurology*. 1989;39(9):1159-1165.

18. National nutrition council. Finnish Nutrition Recommendations: Diet and physical activity in balance. Helsinki: Edita publishing, 2005.

19. Nelson ME, Rejeski WJ, Blair SN, et al. Physical activity and public health in older adults: Recommendation from the American college of sports medicine and the American Heart Association. *Circulation*. 2007;116(9):1094-1105.

20. Komulainen P, Kivipelto M, Lakka TA, et al. Exercise, fitness and cognition—a randomised controlled trial in older individuals: The DR's EXTRA study. *Eur Geriatr Med*. 2010;1:266–72.

21. Dahlin E, Neely AS, Larsson A, Backman L, Nyberg L. Transfer of learning after updating training mediated by the striatum. *Science*. 2008;320:1510–12.

22. Working group appointed by the Finnish medical society Duodecim and the Finnish hypertension society. Hypertension: Current care summary. Helsinki: The Finnish Medical Society Duodecim, 2009.

23. Working group appointed by the Finnish medical society Duodecim and the medical advisory board of the Finnish diabetes society. Diabetes: Current care summary. Helsinki: The Finnish Medical Society Duodecim, 2007.

24. Working group set up by the Finnish medical society Duodecim and Finnish society of internal medicine. Dyslipidaemias: Current care summary. Helsinki: The Finnish Medical Society Duodecim, 2009.

25. Kingston A, Collerton J, Davies K, Bond J, Robinson L, Jagger C. Losing the ability in activities of daily living in the oldest old: A hierarchic disability scale from the Newcastle 85+ study. *PLoS One*. 2012;7(2):e31665.

26. 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.

27. Vaughan L, Leng X, La Monte MJ, Tindle HA, Cochrane BB, Shumaker SA. Functional independence in late-life: Maintaining physical functioning in older adulthood predicts daily life function after age 80. *J Gerontol A Biol Sci Med Sci*. 2016;71 Suppl 1:S79-86.

28. Kulmala J, Nykanen I, Hartikainen S. Frailty as a predictor of all-cause mortality in older men and women. *Geriatr Gerontol Int*. 2014;14(4):899-905.

29. Jacob ME, Yee LM, Diehr PH, et al. Can a healthy lifestyle compress the disabled period in older adults? *J Am Geriatr Soc*. 2016;64(10):1952-1961.

30. Torres JL, Lima-Costa MF, Marmot M, de Oliveira C. Wealth and disability in later life: The English Longitudinal study of Ageing (ELSA). *PLoS One*. 2016;11(11):e0166825.

31. Yu R, Wong M, Chang B, et al. Trends in activities of daily living disability in a large sample of community-dwelling Chinese older adults in Hong Kong: An age-period-cohort analysis. *BMJ Open*. 2016;6(12):e013259-2016-013259.

32. Falk H, Johansson L, Ostling S, et al. Functional disability and ability 75-year-olds: A comparison of two Swedish cohorts born 30 years apart. *Age Ageing*. 2014;43(5):636-641.

33. Pahor M, Guralnik JM, Ambrosius WT, et al. Effect of structured physical activity on prevention of major mobility disability in older adults: The LIFE study randomized clinical trial. *JAMA*. 2014;311(23):2387-2396.

34. Manini TM, Beavers DP, Pahor M, et al. Effect of physical activity on self-reported disability in older adults: Results from the LIFE study. *J Am Geriatr Soc*. 2017;65(5):980-988.

35. Toots A, Littbrand H, Lindelof N, et al. Effects of a high-intensity functional exercise program on dependence in activities of daily living and balance in older adults with dementia. *J Am Geriatr Soc*. 2016;64(1):55-64.

36. Rydwik E, Frandin K, Akner G. Effects of a physical training and nutritional intervention program in frail elderly people regarding habitual physical activity level and activities of daily living--a randomized controlled pilot study. *Arch Gerontol Geriatr*. 2010;51(3):283-289.

TABLES

Table 1. FINGER study population in the intervention and control groups.

Characteristics	Participants with information available	Intervention	Control
Sex (women)	1260	286 (45%)	303 (48%)
Age	1260	69.7 (4.6)	69.4 (4.7)
Education	1258	10.0 (3.5)	10.0 (3.4)
Physical activity at least twice a week	1247	436 (70%)	447 (72%)
Body mass index	1249	28.3 (4.5)	28.1 (4.9)
Diabetes	1253	86 (14%)	79 (13%)
MMSE[a]	1257	26.7 (2.1)	26.8 (2.0)
ADL[b] score baseline	1210	18.2 (2.9)	18.1 (2.4)
SPPB[c] score baseline	1210	10.8 (1.4)	10.8 (1.4)

[a] Mini Mental State Examination (range 0-30, higher score indicates better cognition)

[b] Activities of Daily Living (range 17-85, higher score indicates more disability)

[c] Short Physical Performance Battery (range 0-12, higher score indicates better physical performance)

Table 2. The mean Activities of Daily Living (ADL) and Short Physical Performance Battery (SPPB) scores at baseline and mean change over time.

	Baseline	12 months	24 months
ACTIVITIES OF DAILY LIVING			
ADL disability score at baseline and mean change (SD)[a]			
All (n=1210)	18.1 (2.6)	0.4 (2.0)	0.5 (2.1)
Intervention group (n=603)	18.2 (2.9)	0.3 (2.2)	0.5 (2.2)
Control group (n=607)	18.1 (2.4)	0.5 (1.8)	0.5 (2.0)
% of participants who changed from no disability to at least some disability[b] during 24 months			
Intervention group		17	16
Control group		23	25
PHYSICAL PERFORMANCE			
SPPB score at baseline and mean change (SD)[c]			
All (n=1210)	10.8 (1.4)	NA	-0.2 (1.1)
Intervention group (n=604)	10.8 (1.4)	NA	-0.2 (1.1)
Control group (n=606)	10.8 (1.4)	NA	-0.2 (1.1)

[a] ADL range 17-85, higher score indicating more disability

[b] Score 18 or more refers to at least some difficulties

[c] SPPB range 0-12, higher score indicating better performance

FIGURE LEGENDS

Figure 1: Study flowchart

Figure 2. Change in the Activities of Daily Living (ADL) score during the 2-year intervention period. The figure shows the estimated mean change in the ADL score (range 17-85) from the baseline up to 12 and 24 months (a higher score suggest greater disability). The error bars are confidence intervals. A latent-growth curve modeling approach using all three time points (the baseline, 12 months and 24 months) was used. The p-value from the Wald Test of Parameter Constraints.

SUPPLEMENTARY DATA

Supplementary Table S1. Recorded adherence to intervention components.

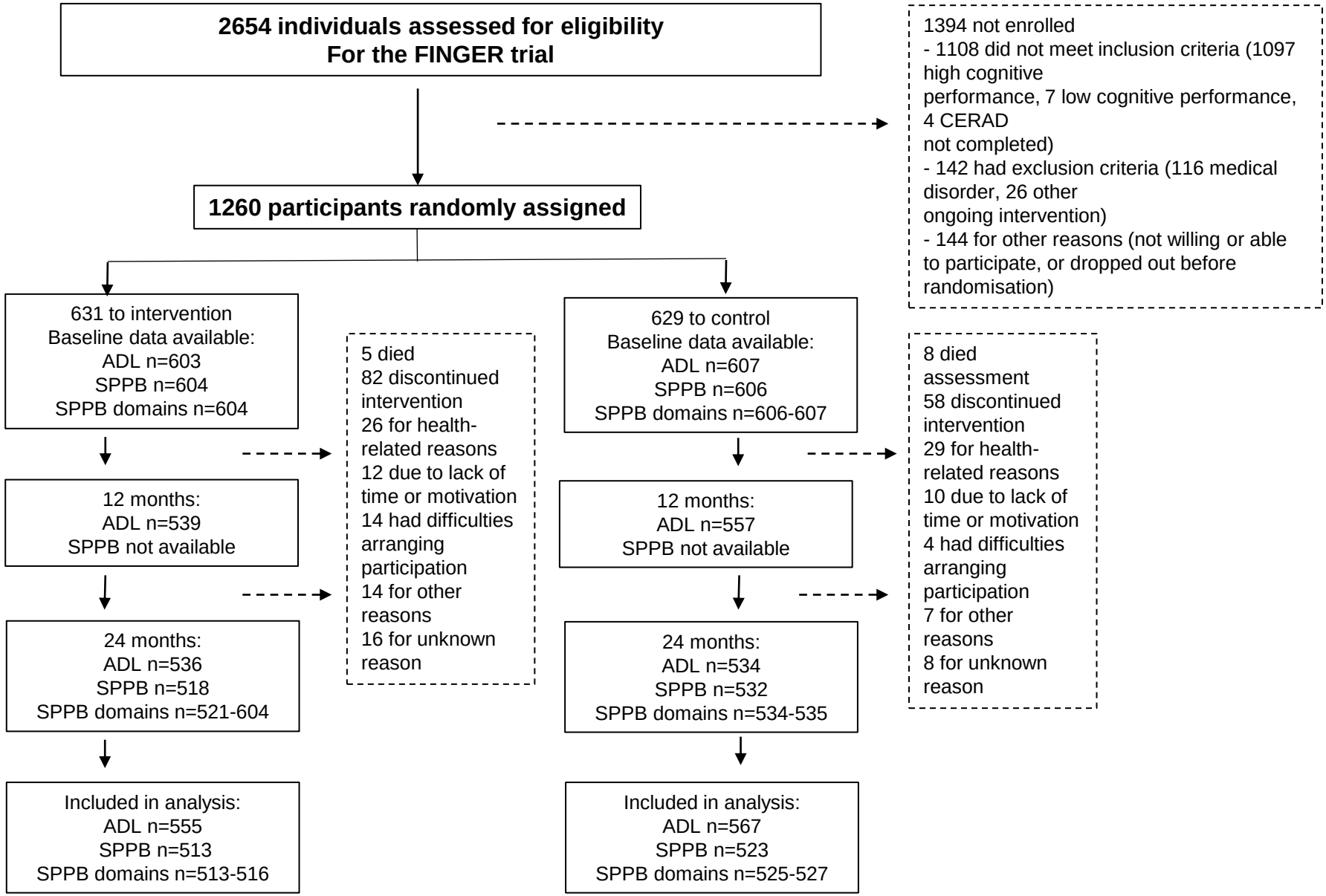
Supplementary Table S2. Percentages of persons with difficulties in daily living activities and physical performance at the baseline and at the 12-month and 24-month follow-up.

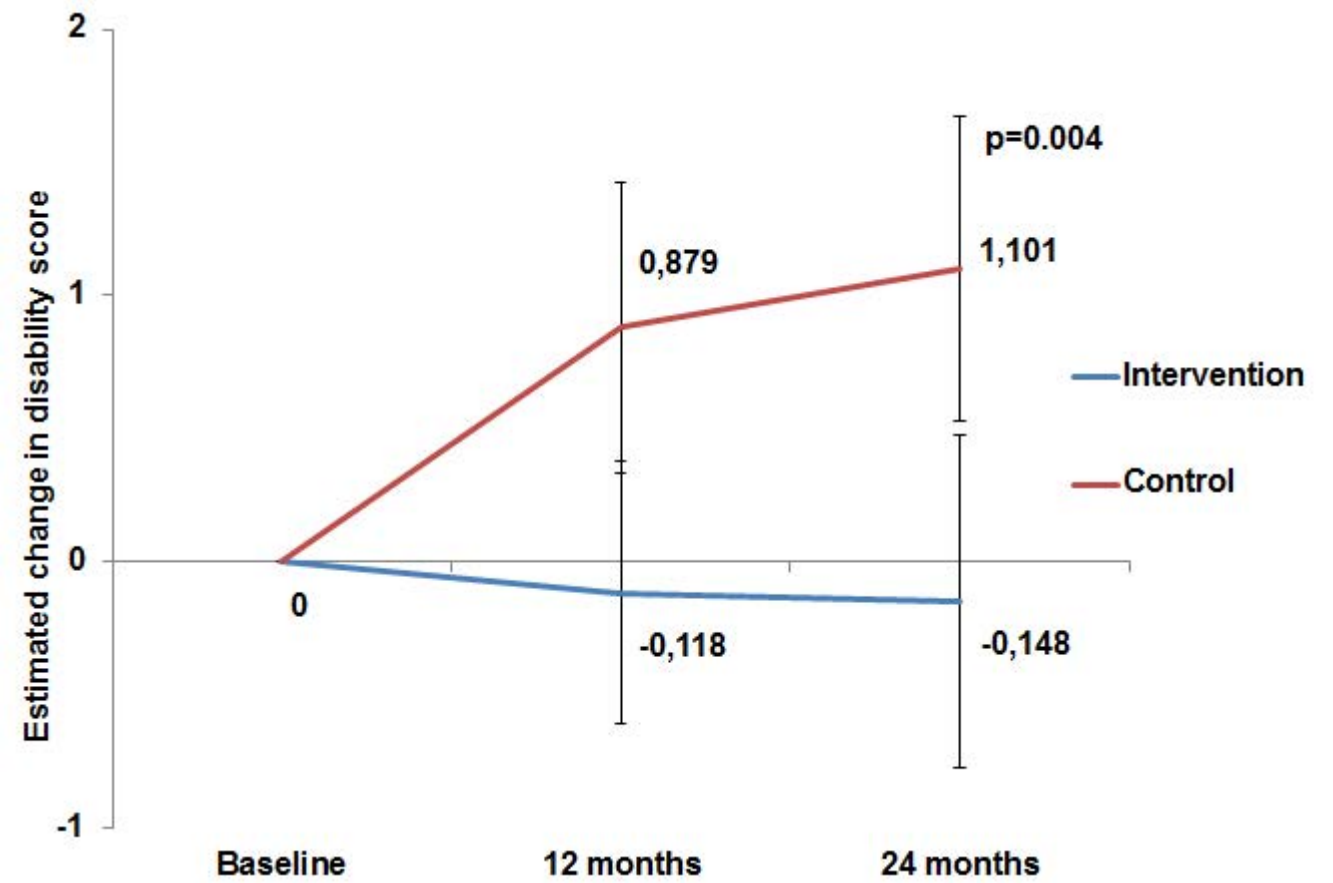
Supplementary Table S3. Distribution of physical performance scores at the baseline and at 24 months.

Supplementary Table S4. Transitions in the chair rise test according to the baseline score and group, and the difference between the intervention and control group (percent with 95% confidence intervals)

Supplementary Table S5. Transitions in the walking test according to the baseline score and group, and the difference between the intervention and control group (percent with 95% confidence intervals)

Supplementary Table S6. Transitions in the balance test according to the baseline score and group, and the difference between the intervention and control group (percent with 95% confidence intervals)


2654 individuals assessed for eligibility
For the FINGER trial
1394 not enrolled
- 1108 did not meet inclusion criteria (1097 high cognitive performance, 7 low cognitive performance, 4 CERAD not completed)
- 142 had exclusion criteria (116 medical disorder, 26 other ongoing intervention)
- 144 for other reasons (not willing or able to participate, or dropped out before randomisation)
1260 participants randomly assigned
631 to intervention
Baseline data available:
ADL n=603
SPPB n=604
SPPB domains n=604
629 to control
Baseline data available:
ADL n=607
SPPB n=606
SPPB domains n=606-607
5 died
82 discontinued intervention
26 for health-related reasons
12 due to lack of time or motivation
14 had difficulties arranging participation
14 for other reasons
16 for unknown reason
8 died
assessment
58 discontinued intervention
29 for health-related reasons
10 due to lack of time or motivation
4 had difficulties arranging participation
7 for other reasons
8 for unknown reason
12 months:
ADL n=539
SPPB not available
12 months:
ADL n=557
SPPB not available
24 months:
ADL n=536
SPPB n=518
SPPB domains n=521-604
24 months:
ADL n=534
SPPB n=532
SPPB domains n=534-535
Included in analysis:
ADL n=555
SPPB n=513
SPPB domains n=513-516
Included in analysis:
ADL n=567
SPPB n=523
SPPB domains n=525-527


2
1
0
-1
Estimated change in disability score
p=0.004
0,879
1,101
Intervention
Control
0
-0,118
-0,148
Baseline
12 months
24 months

Supplementary Table S1. Recorded adherence to intervention components.

No. of sessions	Participants (%)
Nutritional intervention, individual sessions	
0	2.6%
1	3.8%
2-3 (max)	93.6%
Nutritional intervention, group sessions	
0	15.9%
1-3	23.5%
4-6 (max)	60.7%
Cognitive training, individual computer-based training sessions	
0	39.3%
1-72	41.0%
73-144 (max)	19.7%
Cognitive training, group sessions (6 sessions with educational content)	
0	19.8%
1-3	21.9%
4-6 (max)	58.3%
Exercise training, individual testing of resistance training progression (done at months 0, 1, 3, 6, 9, 12, 15, 20 and 24 at the gym training)	
0	13.0%
1-4	24.7%
5-8	62.3%
Exercise training, individual recording of gym training	
0	20.0%
1-40	29.0%
41-80	51.0%
Monitoring of vascular/metabolic factors (recorded attendance in nurse and physician visits)	
0	0.0%
1-5	8.4%
6-9	91.6%

Supplementary Table S2. Percentages of persons with difficulties in daily living activities and physical performance at the baseline and at the 12-month and 24-month follow-up.

	Baseline	12 months	24 months
ACTIVITIES OF DAILY LIVING (ADL)			
Number (%) of participants with difficulties[a] in activities of daily living			
ADL total	436 (36)	466 (43)	461 (43)
Toileting	18 (1)	17 (2)	15 (1)
Eating	6 (1)	10 (1)	7 (1)
Washing	12 (1)	24 (2)	19 (2)
Going to bed	20 (2)	30 (3)	22 (2)
Dressing	31 (3)	38 (3)	29 (3)
Moving inside	20 (2)	29 (3)	28 (3)
Walking in stairs	186 (15)	217 (19)	223 (20)
Cutting toe nails	209 (17)	225 (20)	242 (22)
Taking medications	16 (1)	14 (1)	17 (2)
Use of telephone	35 (3)	36 (3)	36 (3)
Cooking	71 (6)	94 (8)	99 (9)
Light house work	56 (5)	57 (5)	64 (6)
Handling finances	47 (4)	26 (2)	41 (4)
Doing laundry	78 (6)	106 (9)	107 (10)
Using public transportation	48 (4)	65 (6)	67 (6)
Shopping	48 (4)	46 (4)	61 (6)
Heavy house work	268 (22)	307 (27)	311 (28)
PHYSICAL PERFORMANCE			
Number (%) of participants with difficulties in SBBP[b]			
SPPB total	750 (62)	NA	662 (63)
SPPB balance	186 (15)	NA	238 (23)
SPPB walking	54 (5)	NA	58 (6)
SPPB chair rise	706 (58)	NA	599 (57)

[a] ADL total score ranges between 17-85 and score 18 or more refers to at least some disability. In single ADL tasks, score ranges between 1-5 and score 2 or more refers to at least some disability

[b] Short Physical Performance Battery. Total score ranges between 0-12 and score less than 12 refers to at least some difficulties. In single physical performance tasks, score ranges between 0-4 and score less than 4 refers to at least some difficulties.

Supplementary Table S3. Distribution of physical performance scores at the baseline and at 24 months.

	n (%)	
	Baseline	24 months
Balance score		
0	1 (0.1)	5 (0.5)
1	21 (1.7)	32 (3.0)
2	35 (2.9)	52 (4.9)
3	129 (10.7)	149 (14.1)
4	1025 (84.6)	817 (77.4)
Walking score		
0	0 (0)	0 (0)
1	2 (0.1)	1 (0.1)
2	11 (0.9)	10 (1.0)
3	41 (3.4)	47 (4.5)
4	1156 (95.5)	994 (94.5)
Chair rise score		
0	16 (1.3)	20 (1.9)
1	75 (6.2)	81 (7.7)
2	181 (15.0)	146 (13.8)
3	434 (35.8)	352 (33.3)
4	505 (41.7)	457 (43.3)
Total SPPB[a] score		
0	0 (0)	0 (0)
1	0 (0)	0 (0)
2	0 (0)	1 (0.1)
3	3 (0.3)	4 (0.4)
4	4 (0.3)	3 (0.3)
5	4 (0.3)	8 (0.8)
6	8 (0.7)	16 (1.5)
7	16 (1.3)	25 (2.4)
8	38 (3.1)	43 (4.1)
9	88 (7.3)	80 (7.6)
10	195 (16.1)	159 (15.1)
11	394 (32.6)	323 (30.8)
12	460 (38.0)	388 (37.0)

[a] Short Physical Performance Battery. Total score ranges between 0-12 and score less than 12 refers to at least some difficulties. In single physical performance tasks, score ranges between 0-4 and score less than 4 refers to at least some difficulties.

Supplementary Table S4. Transitions in the chair rise test according to the baseline score and group, and the difference between the intervention and control group (percent with 95% confidence intervals)

Baseline score	2 year score	% CTRL	% IV	difference (IV-CTRL)	p-value
0-2	0-2	71.9	62.5	-9.4 (-21.5;2.6)	.125
	3	24.3	31.8	7.5 (-2.1;17.1)	.123
	4	3.8	5.7	1.9 (-0.6;4.5)	.138
3	0-2	24.1	17.5	-6.6 (-13.0;-0.2)	.043[a]
	3	51.8	50.3	-1.5 (-3.5;0.5)	.140
	4	24.1	32.2	8.1 (0.3;15.9)	.041[a]
4	0-2	2.9	3.5	0.6 (-0.7;1.9)	.370
	3	19.7	22.8	3.1 (-3.6;9.7)	.365
	4	77.4	73.8	-3.7 (-11.6;4.3)	.365

[a] Significant difference compared to CTRL –group
Omnibus p=0.288

Supplementary Table S5. Transitions in the walking test according to the baseline score and group, and the difference between the intervention and control group (percent with 95% confidence intervals)

Baseline score	2 year score	% CTRL	% IV	difference (IV-CTRL)	p-value
1-2	1-2	45.1	61.8	16.7 (-40.7;74.2)	.568
	3	46.5	33.8	-12.8 (-56.5;31.0)	.567
	4	8.4	4.5	-4.0 (-18.6;10.7)	.596
3	1-2	10.8	11.9	1.0 (-13.7;15.7)	.891
	3	50.9	52.2	1.4 (-17.9;20.6)	.890
	4	38.3	35.9	-2.4 (-36.3;31.5)	.890
4	1-2	0.2	0.3	0.1 (-0.1;0.3)	.359
	3	2.2	3.2	1.0 (-0.9;2.9)	.320
	4	97.6	96.6	-1.1 (-3.1;1.0)	.320

Omnibus p= 0.669

Supplementary Table S6. Transitions in the balance test according to the baseline score and group, and the difference between the intervention and control group (percent with 95% confidence intervals)

Baseline score	2 year score	% CTRL	% IV	difference (IV-CTRL)	p-value
0-2	0-2	54.4	31.4	-23 (-49.4;3.3)	.087
	3	27.7	32.3	4.6 (-3.6;12.9)	.271
	4	17.9	36.3	18.4 (-3.6;40.3)	.100
3	0-2	23.5	25.1	1.6 (-11.4;14.5)	.813
	3	30.6	31.1	0.5 (-4.0;5.0)	.814
	4	45.9	43.8	-2.1 (-19.5;15.3)	.813
4	0-2	4.4	5.2	0.8 (-0.9;2.4)	.358
	3	10.6	12.1	1.5 (-1.7;4.7)	.356
	4	85	82.7	-2.3 (-7.1;2.5)	.356

Omnibus p= 0.698