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Featured Article

# Adherence to multidomain interventions for dementia prevention: Data from the FINGER and MAPT trials

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## Abstract

**Introduction:** Multidomain interventions, targeting multiple risk factors simultaneously, could be effective dementia prevention strategies, but may be burdensome and not universally acceptable.

**Methods:** We studied adherence rates and predictors in the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability and Multidomain Alzheimer Preventive Trial prevention trials, for all intervention components (separately and simultaneously). Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability participants received a 2-year multidomain lifestyle intervention (physical training, cognitive training, nutritional counseling, and cardiovascular monitoring). Multidomain Alzheimer Preventive Trial participants received a 3-year multidomain lifestyle intervention (cognitive training, physical activity counseling, and nutritional counseling) with either an omega-3 supplement or placebo.

**Results:** Adherence decreased with increasing intervention complexity and intensity: it was highest for cardiovascular monitoring, nutritional counseling, and the omega-3 supplement, and lowest for unsupervised computer-based cognitive training. The most consistent baseline predictors of adherence were smoking and depressive symptoms.

**Discussion:** Reducing participant burden, while ensuring that technological tools are suitable for older individuals, maintaining face-to-face contacts, and taking into account participant characteristics may increase adherence in future trials.

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**Keywords:** Prevention; Trial; Adherence; Multidomain; Intervention

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## 1. Introduction

Modifiable risk factors may account for 35% of dementia cases [1]. A reduction of 10% per decade in the prevalence of several lifestyle risk factors, including obesity, physical inactivity, diabetes, hypertension, and smoking, could potentially reduce the number of worldwide cases of

Alzheimer's disease dementia, the most common form of dementia, in 2050 by around 9 million [2]. However, this projection assumes, in addition to a causal relationship, that implementing lifestyle changes would be acceptable to large numbers of people for long periods of time [3].

Because of the multifactorial nature of dementia, in the past decade, there has been growing interest in multidomain interventions for dementia prevention [3]. These interventions target multiple risk factors simultaneously and are expected to generate additive or synergistic preventive effects, compared with interventions targeting one risk factor alone.

The first large-scale randomized controlled trials (RCTs) of multidomain interventions have been completed in the past few years and have shown mixed results: in the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) trial, an intensive 2-year multidomain intervention targeting diet, exercise, cognitive training, and vascular risk monitoring improved cognition compared with a health education control [4], whereas the longer but less intensive Multidomain Alzheimer Preventive Trial (MAPT) and Prevention of Dementia by Intensive Vascular Care multidomain interventions yielded neutral results from the primary analyses, but suggested that specific subgroups at increased risk of dementia may benefit from such interventions [5,6].

One factor that may influence intervention efficacy is adherence. Health behaviors are notoriously difficult to change, and long-term adherence to lifestyle recommendations is often lower than adherence to medication [7]. Furthermore, intervention periods in dementia prevention trials are typically relatively long (2–7 years, for example), which may further reduce adherence. Adherence may also be affected by the nature, intensity, and method of delivery of interventions, as well as by participant characteristics. However, there are a few data available about adherence to multidomain interventions in older adults [8,9].

The aim of this analysis was to describe and compare adherence to multidomain interventions for the prevention of cognitive decline in two large-scale trials, and within each trial, to identify predictors of adherence to individual components of the intervention and to the multidomain interventions as a whole.

## 2. Methods

### 2.1. Participants and interventions

We analyzed data from the FINGER and MAPT trials, both of which have previously been described in detail [4,5,10,11]. Briefly, FINGER was conducted in six Finnish centers and included 1260 individuals aged 60 to 77 years with a Cardiovascular Risk Factors, Aging, and Incidence of Dementia dementia risk score [12] of 6 or more and cognitive function at the mean level or slightly lower than expected for age, who were recruited from previous population-based national surveys. Participants were ran-

domized to an intensive multidomain intervention or a control group. MAPT was conducted in 13 French centers and included 1680 subjects aged 70 years and older with a Mini-Mental Status Examination (MMSE) [13] score of 24 or more, and a subjective memory complaint, a limitation in one instrumental activity of daily living [14], and/or slow walking speed ( $\leq 0.8$  m/s). MAPT participants were mainly recruited from memory clinics, media campaigns, and healthy aging conferences (conducted in collaboration with pension organizations) [15], and were randomized to one of the following four groups: (1) multidomain lifestyle intervention + omega-3 supplement; (2) multidomain lifestyle intervention + placebo; (3) omega-3 supplement alone; and (4) placebo alone. For the present analysis, we included only subjects assigned to receive a multidomain intervention (with omega-3 supplement or placebo for MAPT subjects).

The interventions tested in each trial are summarized in Fig. 1 and have been described in detail elsewhere [5,10]. The FINGER intervention lasted for 2 years and included computer-based cognitive training, gym-based physical exercise training, nutritional advice, and cardiovascular consultations. Each component of the intervention was delivered separately in group and/or individual sessions or independent training. In MAPT, the multidomain lifestyle intervention lasted for 3 years and involved pencil- and paper-based cognitive training, advice and education about physical activity (including the development of an individualized home-based exercise program), and nutritional advice. It was delivered in group and individual sessions, which simultaneously covered all three components. Furthermore, there were three annual preventive consultations (although adherence to this part of the intervention was not assessed in the current analysis because of the limited number of sessions). All MAPT participants were also asked to take two capsules a day containing either a placebo or a total of 800 mg docosahexaenoic acid and 225 mg eicosapentaenoic acid (placebo/omega-3 assignment was double-blind). Both trials were registered at [ClinicalTrials.gov](https://www.clinicaltrials.gov) (FINGER, NCT01041989; MAPT, NCT00672685) and were approved by the relevant local ethical committees. Written informed consent was obtained from all participants.

### 2.2. Outcomes

Adherence indicators are described in Fig. 1, and were based on attendance at group or individual sessions, completion of cognitive training tasks, and pill counts. For this analysis, participants were considered adherent if they completed at least 66% of the prescribed interventions. We used the same definition for both trials to enable a comparison of results. Although, there is no consensus about the optimal level of participation in lifestyle interventions, this adherence definition was chosen because of its relatively widespread use in the literature, and because it has been suggested to be particularly suitable for behavioral interventions

MAPT		FINGER	
Intervention component	Adherence indicator	Intervention component	Adherence indicator
<b>Multidomain sessions</b> <ul style="list-style-type: none"> <li>• Group sessions comprising:               <ul style="list-style-type: none"> <li>○ Pen and paper-based cognitive training exercises</li> <li>○ Advice and education on physical activity</li> <li>○ Advice and education on improving diet</li> </ul> </li> <li>• 30 minute individual motivational interviews approx. every 6 months, including development of a home-based physical exercise plan</li> </ul>	Attendance at group sessions (N=38) and individual interviews (N=5)	<b>Cognitive training</b> <ul style="list-style-type: none"> <li>• Group sessions</li> <li>• Individual computer-based cognitive training</li> </ul>	Attendance at group sessions (N=6) and completion of computer-based training exercises (N=144)
		<b>Physical exercise</b> <ul style="list-style-type: none"> <li>• Individual gym training sessions</li> <li>• Individual muscle-strength training follow-up sessions</li> </ul>	Attendance at training (N= 80) and follow-up (N=8) sessions
		<b>Nutritional counselling</b> <ul style="list-style-type: none"> <li>• Advice and education about improving diet</li> </ul>	Attendance at individual (N=3) and group (N=6) sessions
<b>Preventive consultations</b> <ul style="list-style-type: none"> <li>• Performed annually by a geriatrician (or other physician)</li> <li>• Monitoring of cardiovascular risk factors, visual and auditory capacities, balance, functional status, nutritional status, oral health, depression and anxiety, and polymedication</li> </ul>	Attendance at consultations (N=3)	<b>Cardiovascular consultations</b> <ul style="list-style-type: none"> <li>• Doctor and nurse consultations</li> <li>• For monitoring of cardiovascular risk factors</li> </ul>	Attendance at doctor (N=2) and nurse (N=7) consultations
<b>Omega-3 supplement or placebo</b> <ul style="list-style-type: none"> <li>• 2 capsules/day</li> </ul>	Pill count		

Fig. 1. Description of intervention components and adherence indicators in the MAPT and FINGER trials. The preventive consultations were not included in the multidomain adherence indicator in MAPT. Abbreviations: FINGER, Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability; MAPT, Multidomain Alzheimer Preventive Trial.

[8,9,16]. Adherence rates were also calculated based on the predefined cutoffs used in each individual trial's primary analysis ( $\geq 50\%$  for FINGER and  $\geq 75\%$  for MAPT). Adherence rates were calculated for the entire follow-up period, except for participants who died or dropped out because of medical reasons, for whom the adherence rate was calculated only until the time of dropout. All sessions were given equal weighting in the adherence indicators, regardless of their timing or whether they were group or individual sessions. This approach enabled us to study the extent to which participants adhered to the interventions that they were assigned, as a whole.

### 2.3. Predictor variables

Candidate baseline predictor variables were selected based on a literature review of factors associated with adherence and known dementia risk factors. The following core set of variables was assessed in both studies: sociodemographics (age, sex, and education), cognitive function (MMSE [13] and Trail Making Test [17], subjective memory performance), depressive symptoms (Zung depression scale [18] score  $\geq 45$  (FINGER) or Geriatric Depression Scale [19] score  $> 5$  (MAPT)), physical performance (Short Phys-

ical Performance Battery [20]), self-reported physical activity (total minutes of exercise per week calculated using the short (MAPT) or modified (FINGER) version of the Minnesota Leisure Time Physical Activity Questionnaire [21,22]), cardiovascular disease, and risk factors (self-reported history of diabetes, stroke, myocardial infarction, heart disease, high blood pressure, and high cholesterol; body mass index; smoking status; alcohol consumption).

In addition, the following predictors were assessed in FINGER only: marital status, income, family history of dementia, employment, participants' initial perception of the study (used as a proxy for self-efficacy), dietary habits (modified recommended Finnish diet score) [23], and previous experience with computers. Several of these variables were also assessed in MAPT as part of a substudy [24] and were used to characterize the population at baseline but not as predictor variables, as they were only available for a subset. Apolipoprotein E (APOE) genotype was also assessed as a predictor in both studies in additional sensitivity analyses.

### 2.4. Statistical analyses

All analyses were conducted in parallel in the two trials. Baseline characteristics were described using means

Table 1  
Baseline characteristics of FINGER and MAPT participants

Characteristics	FINGER (N = 631)	MAPT (N = 837)	P*
Age (y), mean (SD)	69.0 (4.7)	75.3 (4.3)	<.001
Male, N (%)	345 (54.7)	298 (35.6)	<.001
Education, <sup>†</sup> N (%)			<.001
Low	260 (41.5)	175 (21.1)	
Intermediate	208 (33.2)	290 (35.0)	
High	158 (25.2)	364 (43.9)	
MMSE (score/30), mean (SD)	26.7 (2.0)	28.1 (1.6)	<.001
TMT-A (completion time, s), mean (SD)	57.9 (19.9)	46.9 (17.2)	<.001
SPPB <10, N (%)	75 (12.4)	184 (22.1)	<.001
Alcohol intake within European recommended limit, <sup>‡</sup> N (%)	579 (92.3)	632 (83.6)	<.001
Smoking status, N (%)			<.001
Never	356 (57.1)	399 (55.0)	
Former	207 (33.2)	299 (41.2)	
Current	60 (9.6)	27 (3.7)	
BMI, mean (SD)	28.3 (4.5)	26.1 (4.1)	<.001
SBP, mean (SD)	140.2 (16.6)	141.8 (19.6)	.098
DBP, mean (SD)	80.5 (9.7)	78.9 (11.6)	.006
Medical history, N (%)			
Diabetes	85 (13.6)	54 (7.1)	<.001
High BP	424 (67.4)	379 (50.0)	<.001
High cholesterol	410 (65.4)	336 (44.3)	<.001
Stroke	33 (5.3)	33 (4.4)	.435
MI	33 (5.3)	23 (3.0)	.038
Medication use, N (%)			
Antihypertensives	327 (52.4)	363 (48.0)	.100
Antidiabetics	80 (12.8)	49 (6.5)	<.001
Statins	256 (42.2)	259 (34.2)	.002
Single, <sup>§</sup> N (%)	172 (27.3)	267 (42.5)	<.001
Family history of dementia, <sup>§,¶</sup> N(%)	152 (25.9)	158 (28.4)	.346
Good self-rated memory, <sup>#</sup> N (%)	279 (44.4)	197 (23.5)	<.001
Depressive symptoms, <sup>**</sup> N (%)	61 (10.1)	148 (17.8)	<.001
≥100 min physical activity/wk, <sup>††</sup> N (%)	390 (71.0)	675 (81.4)	<.001
Low income, <sup>‡‡</sup> N (%)	147 (24.2)	33 (5.7)	<.001
Previous computer use, N (%)	336 (54.0)	N/A	N/A
Nonpositive perception of study, N (%)	43 (6.8)	N/A	N/A
Low diet score <sup>§§</sup>	248 (39.6)	N/A	N/A

Abbreviations: BMI, Body mass index; BP, blood pressure; DBP, diastolic blood pressure; FINGER, Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability; MAPT, Multidomain Alzheimer Preventive Trial; MI, myocardial infarction; MMSE, Mini-Mental Status Examination; SBP, systolic blood pressure; SD, standard deviation; SPPB, Short Physical Performance Battery; TMT-A, Trail Making Test—part A.

P values <.05 are highlighted in bold.

\*Data shown in italic text indicate that the variable is not directly comparable between the two studies (i.e., the information was not collected in the same way or was only collected in one study).

<sup>†</sup>Low education = primary school certificate or lower; intermediate education = middle/vocational school; high education = high school diploma (e.g., baccalaureate) or higher.

<sup>‡</sup>Alcohol intake ≤7 units/wk for women and ≤14 units/wk for men.

<sup>§</sup>Variables only collected for a subset of MAPT participants (N = 635) who participated in the "Representations and Practices of Prevention in Elderly Populations: Investigating Acceptance to Participate in and Adherence to an Intervention Study for the Prevention of Alzheimer's disease" (ACCEPT) substudy.

<sup>¶</sup>Direct family history, that is, one or both parents.

<sup>#</sup>FINGER: subjective memory rated above average; MAPT: visual analog scale rated <40 (with 0 being perfect memory function and 100 being very bad memory function).

<sup>\*\*</sup>Zung depression score ≥45/80 for FINGER; Geriatric Depression Scale >5/15 for MAPT.

<sup>††</sup>Total minutes of self-reported exercise per week were calculated from the short (MAPT) or modified (FINGER) version of the Minnesota Leisure Time Physical Activity Questionnaire.

<sup>‡‡</sup>Household income ≤20,000€ per year for FINGER, <1000€ per month for MAPT.

<sup>§§</sup>Modified Finnish Recommended Diet score (tertile 1 vs. other tertiles).

(standard deviation) and numbers (%), and were compared between the two trials using *t* tests and rank sum tests for quantitative variables and  $\chi^2$  tests for qualitative variables.

Predictors of adherence (defined as completing ≥66% of interventions) were assessed in multilevel logistic regression

models containing a random intercept to take into account within-center correlations. Identical multivariate models were run for each adherence indicator, and included all variables that were significantly ( $P < .05$ ) associated with at least one adherence indicator in univariate analyses, or that

were considered to be important predictors of adherence in the literature. The primary analyses included the core set of predictor variables available in both trials. *APOE* genotype was tested as a predictor variable in sensitivity analyses only, because of a high rate of missing data. The additional FINGER predictor variables were included in secondary analyses, and the alternative adherence definitions were used in sensitivity analyses. No imputation of missing data was performed; each model therefore included only subjects with no missing data for the relevant outcome measure (adherence indicator(s)) and independent variables.

Analyses were performed using Stata version 14.1 (Stata-Corp LP, College Station, TX, USA).

### 3. Results

#### 3.1. Participants

Eight hundred thirty-seven MAPT subjects and 631 FINGER subjects were included in the analysis, of whom 77% and 86%, respectively, completed the full follow-up period (3 years for MAPT and 2 years for FINGER). There were significant differences between the two trials' participants for nearly all the baseline characteristics assessed (Table 1). Notably, MAPT participants were older, with poorer physical performance, but a higher level of education, and better objective cognitive performance. FINGER participants had more cardiovascular risk factors and were more predominantly male.

#### 3.2. Adherence rates

In FINGER, adherence was highest for cardiovascular monitoring (94.6% were adherent using the FINGER prespecified definition, and 92.9% were adherent using the common 66% definition of adherence) and lowest for cognitive training (47.2% and 24.7%, for each definition, respectively), and 38.9% (19% using the common adherence definition) of participants simultaneously adhered to all four intervention components (Fig. 2). In MAPT, adherence was higher for the omega-3/placebo capsules (71.5% were adherent using the MAPT prespecified definition and 76.1% using the common 66% definition) than for the multidomain sessions (53.5% and 64.4%), and 50.7% (61.1% with the common definition) of subjects simultaneously adhered to both the supplement/placebo and the multidomain sessions. In addition, 90.1%, 71.9%, and 62.3% of MAPT subjects attended the baseline, 1- and 2-year cardiovascular consultations, respectively.

#### 3.3. Factors associated with adherence to individual intervention components

No baseline factors were associated with adherence to the FINGER cardiovascular consultations (Table 2;

Supplementary Fig. 1). However, for the nutrition component, current smoking (odds ratio [OR] 0.32 [95% confidence interval [CI] 0.16–0.61],  $P = .001$ ) was associated with poorer adherence, and obesity (2.35 [1.28–4.30],  $P = .006$ ) and a history of stroke (5.22 [1.13–24.05],  $P = .034$ ) were associated with better adherence. For physical activity, older age (0.95 [0.91–0.99],  $P = .027$ ), poorer global cognitive function (0.66 [0.44–0.99],  $P = .046$ ), current smoking (0.47 [0.23–0.96],  $P = .038$ ), and a history of diabetes (0.49 [0.27–0.90],  $P = .022$ ) were associated with poorer adherence, whereas 100 minutes or more of self-reported physical activity (1.90 [1.20–3.00],  $P = .006$ ) were associated with better adherence. For cognitive training, older age (0.93 [0.89–0.98],  $P = .009$ ) and current smoking (0.24 [0.09–0.70],  $P = .008$ ) were associated with poorer adherence, and an intermediate level of education (1.95 [1.18–3.23],  $P = .009$ ) and 100 minutes or more of self-reported physical activity (1.86 [1.08–3.21],  $P = .026$ ) were associated with better adherence.

In MAPT (Table 3; Supplementary Fig. 1), poorer global cognitive function (0.64 [0.44–0.95],  $P = .024$ ), depressive symptoms (0.47 [0.30–0.72],  $P = .001$ ), being overweight (0.55 [0.37–0.83],  $P = .004$ ), and a history of high blood pressure (0.69 [0.48–1.00],  $P = .047$ ) were associated with poorer adherence to the multidomain intervention. Depressive symptoms (0.43 [0.26–0.70],  $P = .001$ ) were also associated with poorer adherence to omega-3/placebo, whereas an intermediate level of education was associated with better adherence to omega-3/placebo (2.04 [1.15–3.61],  $P = .014$ ).

In secondary FINGER analyses including additional predictor variables (Supplementary Table 1), marital status and diet scores were not associated with adherence to any intervention components, but low income was associated with poorer adherence to the nutrition component (0.34 [0.19–0.62],  $P < .001$ ), and previous computer use (2.26 [1.30–3.94],  $P = .004$ ) and a nonpositive perception of the study (0.19 [0.04–0.90],  $P = .036$ ) were, respectively, associated with better and poorer adherence to cognitive training. Furthermore, in these fully adjusted models, age, education, and cognitive function were no longer associated with adherence to any intervention components, whereas other results mostly remained stable.

In sensitivity analyses using each trial's prespecified definition of adherence (i.e.,  $\geq 50\%$  for FINGER and  $\geq 75\%$  for MAPT), there were some differences in results, notably in FINGER, with poorer executive function becoming significantly associated with poorer adherence to all intervention components except cardiovascular monitoring (Supplementary Table 2). MAPT results remained relatively stable, however (Supplementary Table 3).

In a further sensitivity analysis, we also included *APOE* genotype as a predictor variable, but there was no significant association with adherence to any intervention components in either trial (data not shown).

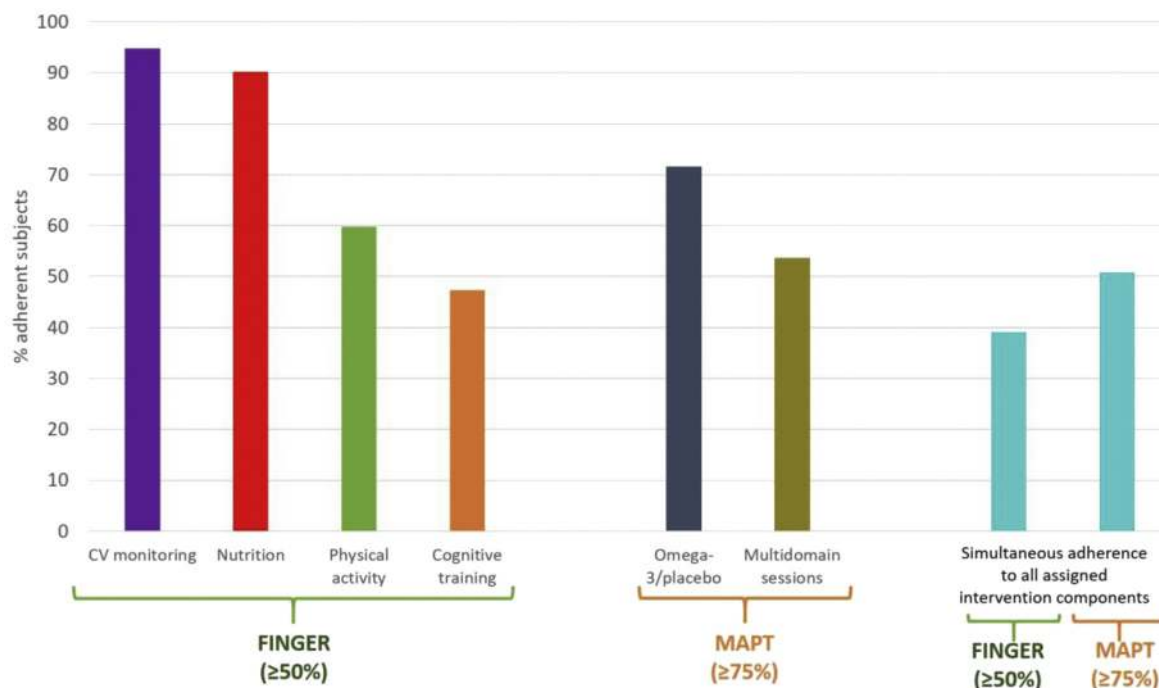


Fig. 2. Adherence rates in the FINGER and MAPT trials: proportion of subjects completing each trial's predefined level of adherence ( $\geq 50\%$  for FINGER,  $\geq 75\%$  for MAPT). Abbreviations: FINGER, Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability; MAPT, Multidomain Alzheimer Preventive Trial.

### 3.4. Factors associated with simultaneous adherence to all intervention components

Older age (0.91 [0.86–0.97],  $P = .002$ ) and current smoking (0.32 [0.11–0.95],  $P = .039$ ) were associated with poorer simultaneous adherence to all FINGER intervention components in the primary analysis, whereas an intermediate level of education (2.05 [1.18–3.58],  $P = .011$ ) was associated with better simultaneous adherence (Table 4; Supplementary Fig. 1). In the MAPT primary analysis, depressive symptoms (0.47 [0.30–0.73],  $P = .001$ ) and current smoking (0.37 [0.15–0.94],  $P = .036$ ) were associated with poorer simultaneous adherence to both intervention components (Table 4; Supplementary Fig. 1).

In sensitivity analyses using each study's predefined definition of simultaneous adherence (Supplementary Tables 3 and 4), for FINGER, in addition to the associations observed in the main model, poorer executive function (1-second increase in Trail Making Test A score: 0.98 [0.97–1.00],  $P = .005$ ) and physical performance (Short Physical Performance Battery  $< 10$ : 0.24 [0.24–0.95],  $P = .036$ ) became associated with poorer adherence. Results were similar to the primary analysis for MAPT, except that poorer global cognition (MMSE  $< 28$ ) became significantly associated with poorer adherence (0.64 [0.44–0.93],  $P = .019$ ).

In a further sensitivity analysis, we also included *APOE* genotype as a predictor variable, but there was

no significant association with simultaneous adherence to all intervention components in either trial (data not shown).

In a secondary FINGER analysis, including additional predictor variables in the original model (Supplementary Table 5), age remained significantly associated with adherence, but current smoking and education did not. Furthermore, history of diabetes became significantly associated with adherence, but there was no association with the additional variables. A nonpositive perception of the study, however, was borderline significantly associated with poorer adherence (0.12 [0.01–1.02],  $P = .053$ ).

## 4. Discussion

Successful dementia prevention may require adherence to a variety of interventions, including medical consultations, medication or supplement use, dietary changes, physical activity, and cognitive training, but there are a few data so far about adherence to such interventions in this context. In two of the longest and largest multidomain trials completed to date for the prevention of cognitive decline, the proportion of subjects who adhered to at least 66% of individual intervention components ranged from 25% to 93%, with higher rates for less burdensome components. The proportion of individuals who were adherent to all their assigned

Table 2

Multivariate multilevel logistic regression analyses showing associations between baseline characteristics and adherence to individual components of the FINGER intervention (adherence defined as completion of at least 66% of the intervention component)

Characteristics	Cardiovascular consultations (N = 562)		Nutrition (N = 555)		Physical activity (N = 560)		Cognitive training (N = 558)	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
<b>Sociodemographic variables</b>								
Age	0.98 (0.89–1.08)	.673	0.99 (0.94–1.04)	.681	0.95 (0.91–0.99)	<b>.027</b>	0.93 (0.89–0.98)	<b>.009</b>
Female (vs. male)	1.77 (0.65–4.80)	.265	1.41 (0.89–2.24)	.146	0.73 (0.47–1.12)	.153	1.25 (0.77–2.04)	.368
Education		.187		.634		.340		<b>.034</b>
Low (ref)	1.00		1.00		1.00		1.00	
Intermediate	2.54 (0.91–7.15)	.077	1.26 (0.78–2.05)	.339	1.37 (0.87–2.16)	.173	1.95 (1.18–3.23)	<b>.009</b>
High	1.76 (0.59–5.24)	.310	1.11 (0.65–1.89)	.712	1.02 (0.62–1.69)	.933	1.42 (0.79–2.55)	.237
<b>Cognition, mood, physical status</b>								
MMSE <28 (vs. ≥28)	1.36 (0.56–3.32)	.500	1.21 (0.78–1.87)	.388	0.66 (0.44–0.99)	<b>.046</b>	1.35 (0.85–2.13)	.200
TMT-A (per second increase)	0.98 (0.96–1.01)	.148	0.99 (0.98–1.00)	.083	0.99 (0.98–1.00)	.246	0.99 (0.98–1.01)	.316
Presence of depressive symptoms	1.36 (0.34–5.50)	.664	0.55 (0.29–1.05)	.072	0.32 (0.16–0.64)	<b>.001</b>	0.89 (0.40–1.96)	.768
SPPB <10	0.70 (0.19–2.52)	.585	0.69 (0.36–1.32)	.263	0.70 (0.37–1.34)	.282	0.48 (0.21–1.10)	.081
<b>Lifestyle variables</b>								
Smoking		.480		<b>.002</b>		.050		<b>.027</b>
Never smoked (ref)	1.00		1.00		1.00		1.00	
Former smoker	0.62 (0.24–1.61)	.326	0.89 (0.55–1.45)	.643	0.66 (0.42–1.03)	.067	0.99 (0.59–1.65)	.966
Current smoker	0.51 (0.14–1.87)	.309	0.32 (0.16–0.61)	<b>.001</b>	0.47 (0.23–0.96)	<b>.038</b>	0.24 (0.09–0.70)	<b>.008</b>
Alcohol within European recommended weekly limit	2.89 (0.82–10.22)	.100	0.84 (0.36–1.95)	.687	1.26 (0.59–2.67)	.551	1.06 (0.44–2.60)	.890
Physical activity		.175		.267		<b>.023</b>		.082
< 100 min/wk	1.00		1.00		1.00		1.00	
≥ 100 min/wk	1.92 (0.73–5.08)	.186	1.42 (0.87–2.32)	.162	1.90 (1.20–3.00)	<b>.006</b>	1.86 (1.08–3.21)	<b>.026</b>
Missing data	0.76 (0.25–2.29)	.620	0.98 (0.50–1.91)	.957	1.73 (0.87–3.41)	.116	1.50 (0.65–3.44)	.342
BMI		.104		<b>.022</b>		.321		.537
18.5–24.9 (ref)	1.00		1.00		1.00		1.00	
25–29.9	0.69 (0.24–1.93)	.475	1.43 (0.87–2.34)	.157	0.91 (0.57–1.48)	.712	1.15 (0.66–1.99)	.616
≥30	2.63 (0.62–11.17)	.190	2.35 (1.28–4.30)	<b>.006</b>	1.31 (0.76–2.26)	.332	1.41 (0.77–2.59)	.271
<b>Cardiovascular variables</b>								
History of diabetes	0.44 (0.14–1.42)	.170	0.66 (0.36–1.22)	.185	0.49 (0.27–0.90)	<b>.022</b>	0.79 (0.39–1.59)	.511
History of high BP	1.50 (0.62–3.63)	.363	0.95 (0.60–1.49)	.812	0.99 (0.65–1.52)	.981	1.56 (0.95–2.55)	.077
History of high cholesterol	1.87 (0.77–4.53)	.167	1.12 (0.71–1.75)	.628	1.42 (0.94–2.14)	.098	1.01 (0.63–1.62)	.967
History of stroke	—	—	5.22 (1.13–24.05)	<b>.034</b>	1.29 (0.51–3.27)	.585	0.41 (0.11–1.56)	.191
History of MI	0.58 (0.14–2.48)	.467	0.77 (0.33–1.83)	.559	0.91 (0.36–2.26)	.834	0.78 (0.27–2.29)	.652

Abbreviations: BMI, Body mass index; BP, blood pressure; CI, confidence interval; FINGER, Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability; MI, myocardial infarction; MMSE, Mini-Mental Status Examination; OR, odds ratio; SPPB, Short Physical Performance Battery; TMT-A, Trail Making Test—part A.

NOTE. Low education = primary school certificate or lower; intermediate education = middle/vocational school; high education = high school diploma (e.g., baccalaureate) or higher.

P values <.05 are highlighted in bold.

interventions ranged from 19% to 61% using the 66% definition of adherence, and 39% to 51% using each trial's pre-specified definition, and decreased with increasing intervention complexity and intensity. Adherence was also influenced by participant characteristics, with depressive symptoms and current smoking being the most consistent predictors of poor adherence, but results varied across intervention components and trials.

Long-term adherence rates were excellent for cardiovascular monitoring and nutritional counseling in FINGER, and very good for the dietary supplement in MAPT. These were the least "active" components of the two trials' interventions, but greater burden was not necessarily a major barrier to adherence, because in FINGER, around half of the participants completed at least 66% of the exercise ses-

sions, and 74% of MAPT participants completed at least 75% of the multidomain sessions during the intensive intervention phase during the first 2 months of the trial (data not shown). Difficulties in accessing primary care in Finland could also contribute the high adherence to the cardiovascular consultations in FINGER. Furthermore, adherence in FINGER was highest to individual visits (both cardiovascular consultations and nutritional counseling) where the timing of the visit was scheduled together with the participant (data not shown). It is unknown what level of adherence is needed for a given intervention to have an effect on cognition. Thus, the cutoffs we used to define adherence were somewhat arbitrary, and further work is required to determine the impact of intervention adherence on efficacy.



Table 3

Multivariate multilevel logistic regression analyses showing associations between baseline characteristics and adherence to individual MAPT interventions (adherence defined as completion of at least 66% of the intervention component)

Characteristics	Multidomain intervention (N = 692)		Omega-3/placebo (N = 647)	
	OR (95% CI)	P	OR (95% CI)	P
<b>Sociodemographic variables</b>				
Age	0.98 (0.94–1.02)	.399	0.97 (0.92–1.01)	.159
Female (vs. male)	1.24 (0.83–1.86)	.293	0.63 (0.39–1.03)	.066
Education		.923		<b>.035</b>
Low (ref)	1		1	
Intermediate	1.01 (0.62–1.64)	.980	2.04 (1.15–3.61)	<b>.014</b>
High	0.93 (0.56–1.53)	.778	1.27 (0.73–2.21)	.402
<b>Cognition, mood, physical status</b>				
MMSE <28 (vs. ≥28)	0.64 (0.44–0.95)	<b>.024</b>	1.10 (0.69–1.76)	.692
TMT-A (per second increase)	0.99 (0.98–1.00)	.122	0.99 (0.98–1.00)	.212
Presence of depressive symptoms	0.47 (0.30–0.72)	<b>.001</b>	0.43 (0.26–0.70)	<b>.001</b>
SPPB <10	0.77 (0.50–1.18)	.227	0.83 (0.50–1.36)	.462
<b>Lifestyle variables</b>				
Smoking		.125		.328
Never smoked (ref)	1		1	
Former smoker	1.12 (0.76–1.66)	.567	1.11 (0.70–1.77)	.645
Current smoker	0.44 (0.18–1.08)	.073	0.53 (0.20–1.41)	.206
Alcohol within recommended weekly limit	0.74 (0.45–1.22)	.237	1.03 (0.58–1.81)	.931
≥100 min physical activity/wk	1.08 (0.69–1.71)	.732	0.75 (0.44–1.30)	.308
BMI		<b>.014</b>		.763
18.5–24.9 (ref)	1		1	
25–29.9	0.55 (0.37–0.83)	<b>.004</b>	0.86 (0.54–1.36)	.513
≥30	0.66 (0.39–1.13)	.127	0.83 (0.44–1.56)	.561
<b>Cardiovascular variables</b>				
History of diabetes	0.73 (0.38–1.38)	.327	0.96 (0.43–2.13)	.922
History of high BP	0.69 (0.48–1.00)	<b>.047</b>	0.82 (0.53–1.26)	.371
History of high cholesterol	1.11 (0.77–1.59)	.583	0.93 (0.61–1.42)	.748
History of stroke	1.18 (0.51–2.75)	.696	0.78 (0.31–1.99)	.605
History of MI	1.80 (0.59–5.46)	.299	0.79 (0.23–2.67)	.706

Abbreviations: BMI, Body mass index; BP, blood pressure; CI, confidence interval; MAPT, Multidomain Alzheimer Preventive Trial; MI, myocardial infarction; MMSE, Mini-Mental Status Examination; OR, odds ratio; SPPB, Short Physical Performance Battery; TMT-A, Trail Making Test–part A.

NOTE. Low education = primary school certificate or lower; intermediate education = middle/vocational school; high education = high school diploma (e.g., baccalaureate) or higher.

P values <.05 are highlighted in bold.

Lower cognitive training adherence in FINGER could be explained by several factors. First, the cognitive training was computer-based and only 54% of participants reported previous computer experience at baseline. Indeed, this was a strong predictor of adherence to both cognitive training and the multidomain intervention as a whole, and not having a computer was the main self-reported reason for not participating in the cognitive training (data not shown). Second, this was the least supervised component of the FINGER intervention, because participants were primarily asked to complete the cognitive training independently. Older people are not necessarily averse to cognitive training in itself, because 64% of MAPT participants adhered to the multidomain sessions, which included supervised pen- and paper-based cognitive training exercises, and 59% of FINGER participants adhered to group cognitive training sessions (data not shown). Therefore, despite the logistical burden, future trials should not underestimate the necessity of supervised

interventions, particularly when using techniques or technologies with which older participants may not be familiar. However, with increasing Internet skills in older populations in recent years [25], computer-based interventions might now be more feasible in this age group. Insight into the acceptability of a preventive Internet intervention in older European adults will be provided by the recently completed Healthy Ageing Through Internet Counselling in the Elderly trial [26]. Initial qualitative results suggest that human support may be crucial for the success of this kind of intervention in older age groups [27].

Identifying factors associated with adherence can help to improve implementation of prevention programs and understand potential biases in research studies [9,28]. There are few studies of predictors of adherence to multidomain interventions in older populations [9,29,30], and none have simultaneously investigated adherence to individual components and multidomain interventions as a whole, or

Table 4

Multivariate multilevel logistic regression models showing associations between baseline characteristics and simultaneous adherence to all intervention components in MAPT and FINGER (adherence defined as completion of at least 66% of the intervention component)

Characteristics	Simultaneous adherence to all components of FINGER intervention (N = 558)		Simultaneous adherence to both components of MAPT intervention (N = 647)	
	OR (95% CI)	P	OR (95% CI)	P
<b>Sociodemographic variables</b>				
Age	0.91 (0.86–0.97)	<b>.001</b>	0.97 (0.93–1.02)	.211
Female (vs. male)	1.08 (0.63–1.84)	.789	0.94 (0.63–1.40)	.754
Education		<b>.033</b>		.543
Low (ref)	1.00		1.00	
Intermediate	2.08 (1.20–3.63)	<b>.010</b>	1.23 (0.76–2.00)	.405
High	1.65 (0.86–3.14)	.131	1.00 (0.62–1.63)	.993
<b>Cognition, mood, physical status</b>				
MMSE <28 (vs. ≥28)	1.29 (0.78–2.13)	.330	0.76 (0.52–1.11)	.159
TMT-A (per second increase)	1.00 (0.98–1.01)	.654	0.99 (0.98–1.00)	.160
Presence of depressive symptoms	0.88 (0.37–2.08)	.768	0.47 (0.30–0.73)	<b>.001</b>
SPPB <10	0.51 (0.20–1.31)	.164	0.82 (0.53–1.27)	.373
<b>Lifestyle variables</b>				
Smoking		.118		.100
Never smoked (ref)	1.00		1.00	
Former smoker	0.82 (0.46–1.46)	.498	1.00 (0.68–1.46)	.986
Current smoker	0.32 (0.11–0.95)	<b>.039</b>	0.37 (0.15–0.94)	<b>.036</b>
Alcohol within recommended weekly limit	1.43 (0.52–3.96)	.486	0.97 (0.60–1.55)	.889
≥100 min physical activity/wk (vs. <100 min)*	1.44 (0.79–2.60)	.231	1.07 (0.68–1.67)	.782
BMI		.486		.435
18.5–24.9 (ref)	1.00		1.00	
25–29.9	1.22 (0.66–2.24)	.533	0.78 (0.53–1.15)	.208
≥30	1.51 (0.77–2.95)	.232	0.81 (0.48–1.37)	.436
<b>Cardiovascular variables</b>				
History of diabetes	0.54 (0.23–1.24)	.145	0.55 (0.29–1.04)	.065
History of high BP	1.59 (0.92–2.74)	.097	0.85 (0.59–1.21)	.363
History of high cholesterol	1.42 (0.84–2.40)	.195	0.97 (0.68–1.38)	.868
History of stroke	0.55 (0.14–2.20)	.396	0.89 (0.39–2.04)	.787
History of MI	0.74 (0.21–2.61)	.636	0.78 (0.28–2.13)	.623

Abbreviations: BMI, Body mass index; BP, blood pressure; CI, confidence interval; FINGER, Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability; MAPT, Multidomain Alzheimer Preventive Trial; MI, myocardial infarction; MMSE, Mini-Mental Status Examination; OR, odds ratio; SPPB, Short Physical Performance Battery; TMT-A, Trail Making Test–part A.

NOTE. Low education = primary school certificate or lower; intermediate education = middle/vocational school; high education = high school diploma (e.g., baccalaureate) or higher. Adherence to all components of the FINGER intervention means completing ≥66% of the cardiovascular, nutrition, physical exercise, and cognitive training components. Adherence to both components of the MAPT intervention means attending ≥66% of the multidomain sessions and taking ≥66% of the placebo or omega-3 supplement capsules.

P values <.05 are highlighted in bold.

\*For FINGER, the model also included a category for individuals with missing data for this variable (N = 69; data not shown).

evaluated a common set of candidate predictors of adherence across different trials. Results of previous analyses have varied, probably because of, in particular, differences in intervention strategies, study populations, and methodologies.

Depressive symptoms were significantly associated with poorer adherence to both intervention components in MAPT, and with physical activity, and, to a lesser extent, nutrition in FINGER. Some previous studies have also observed an association between depression and decreased adherence to physical exercise [31,32], and it is a well-known predictor of medication/supplement nonadherence [33,34].

Self-efficacy is one of the most important predictors of adherence to lifestyle interventions, particularly physical ac-

tivity, in older adults [28,31,35–38]. It was not measured in either MAPT or FINGER, but in FINGER, participants' initial perception of the study, which is the closest proxy, was not significantly associated with adherence to physical activity, although it was associated with adherence to cognitive training and with simultaneous adherence to all intervention components.

Cognition might also be expected to affect adherence. However, only some [9,39,40], but not all [29,41], previous studies have found an association. Likewise, associations between cognition and adherence were inconsistent in our analysis, and in particular appeared to be dependent on the definition of adherence used.

Concerning health behaviors, current smoking is a well-known predictor of poorer adherence to both lifestyle and

drug/supplements [28,33,42,43], and was one of the most consistent predictors of (poor) adherence in our analyses. As also expected [30,36,44], increased baseline physical activity was associated with better adherence to the FINGER physical activity intervention. It was also associated with better adherence to the FINGER cognitive training, supporting previous studies, which have found physical activity to predict adherence to various lifestyle interventions [29,45,46]. However, it was not associated with any MAPT adherence indicators, perhaps because of the self-reported nature of the physical activity data and the cutoff used to distinguish between physically active and inactive participants, which may not have been optimal.

Sociodemographic factors are inconsistent predictors of adherence to lifestyle interventions in the literature, and this was reflected in our results: age, sex, and education were not consistent strong predictors of adherence, particularly in fully adjusted models, but females were significantly more likely to adhere to the nutrition sessions in FINGER, as in previous studies [9,30,42,46]. An intermediate (compared with low) level of education was significantly associated with poorer adherence in some analyses, but the secondary FINGER analyses suggested that in fact this could be a reflection of low income. The perceived expense of maintaining a healthy lifestyle, particularly a healthy diet, could conceivably influence the decision to make lifestyle changes for some participants, notably those with low income. Indeed, financial costs were identified as a recurring barrier to the uptake and maintenance of various healthy behaviors during midlife in a recent systematic review [47].

The strengths of this study include the original nature of the data, the large sample sizes, the use of multivariate analyses adjusted for numerous factors (in contrast to some previous studies [30,38,42]), including a core set of variables that were common across two trials. Furthermore, we used a (modified) intention to treat definition of adherence [28], meaning that we did not artificially inflate estimates of adherence rates through our handling of dropouts. However, our analysis also has some limits, including its exploratory nature, the methodological differences between the two trials, and the fact that not all relevant predictors of adherence, notably self-efficacy, were assessed. Also, we only assessed baseline predictors of adherence, but it may also be important to consider variables measured at different time points, notably for those relating to health status, which is likely to change over time, particularly in older populations, and which is likely to influence adherence. Our results are also dependent on the definition of adherence, although they remained relatively stable in sensitivity analyses using alternative definitions. Furthermore, for some intervention components, for example the nutrition components in both trials, we simply measured study attendance, rather than whether participants were actually making lifestyle

changes. However, the two are likely to be strongly related [48,49]. Also, we only studied a selected population of individuals who had agreed to take part in a long-term multidomain lifestyle intervention trial. Finally, we examined adherence for the entire follow-up period, because we were interested in whether individuals adhered long term to the interventions they were prescribed, and also, intervention intensity over time differed between the two trials, which would have made it challenging to perform a comparable analysis. However, there may be certain periods during long-term lifestyle interventions for which adherence may be more critical than others, and also predictors of adherence may change over time [28,36]. These issues require further study.

## 5. Conclusion

Multidomain interventions may be burdensome and not universally acceptable. Adherence to such interventions depends on participant characteristics, as well as intervention type, intensity, and method of delivery. Future trials should consider ways to reduce participant burden and increase adherence. The development of interventions based on Internet or smartphone and the use of connected devices could decrease the burden of multidomain interventions, but they may not yet be universally acceptable in older populations, thus potentially compromising uptake and adherence in some individuals, and further enhancing inequalities in access to prevention programs. Furthermore, face-to-face contact appears to be particularly important in older populations, both to facilitate intervention adherence and stimulate social interactions, which may be a valuable dementia prevention strategy [1]. A more personalized approach to multidomain interventions could also be envisaged, in which participants could be offered interventions targeting their own specific risk factors, and extra motivational interventions could be included for individuals at most risk of nonadherence, notably smokers and those with depressive symptoms. Finally, it may be helpful to emphasize, particularly for those with low socioeconomic status, that lifestyle changes can be made without incurring major expenses.

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## Supplementary Data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.jalz.2019.03.005>.

### RESEARCH IN CONTEXT

1. **Systematic review:** The literature was reviewed using PubMed and the authors' own files and reference lists. There have been few studies of adherence to multidomain interventions in older adults, particularly not in the context of dementia prevention. Conclusions from previous studies are limited by variations in adherence definitions and candidate predictor variables, and, sometimes, unadjusted statistical analyses.
2. **Interpretation:** Adherence to multidomain interventions depends on participant characteristics, as well as intervention type, intensity, and method of delivery. Unsupervised interventions and use of new technologies may be challenging in older populations. Current smoking and depressive symptoms were consistent predictors of adherence, across both trials and when using different definitions of adherence and adjustment models.
3. **Future directions:** Future trials should consider ways to reduce participant burden, while maintaining face-to-face contacts and ensuring that technological tools are suitable for older individuals. Extra motivational interventions could be included for individuals at most risk of nonadherence.

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