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Original Research

The Effect of Multidomain Interventions on Global Cognition, Symptoms of Depression and Apathy – A Pooled Analysis of Two Randomized Controlled Trials

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Abstract

BACKGROUND: Cardiovascular risk factors and lifestyle factors are associated with an increased risk of cognitive decline and dementia in observational studies, and have been targeted by multidomain interventions.

OBJECTIVES: We pooled individual participant data from two multi-domain intervention trials on cognitive function and symptoms of depression to increase power and facilitate subgroup analyses.

DESIGN: Pooled analysis of individual participant data.

SETTING: Prevention of Dementia by Intensive Vascular Care trial (preDIVA) and Multidomain Alzheimer Preventive Trial (MAPT).

PARTICIPANTS: Community-dwelling individuals, free from dementia at baseline.

INTERVENTION: Multidomain interventions focused on cardiovascular and lifestyle related risk factors.

MEASUREMENTS: Data on cognitive functioning, depressive symptoms and apathy were collected at baseline, 2 years and 3-4 years of follow-up as available per study. We analyzed crude scores with linear mixed models for overall cognitive function (Mini Mental State Examination [MMSE]), and symptoms of depression and apathy (15-item Geriatric Depression Scale). Prespecified subgroup analyses were performed for sex, educational level, baseline MMSE <26, history of hypertension, and history of stroke, myocardial infarction and/or diabetes mellitus.

RESULTS: We included 4162 individuals (median age 74 years, IQR 72, 76) with a median follow-up duration of 3.7 years (IQR 3.0 to 4.1 years). No differences between intervention and control groups were observed on change in cognitive functioning scores and symptoms of depression and apathy scores in the pooled study population. The MMSE declined less in the intervention groups in those with MMSE <26 at baseline (N=250; MD: 0.84; 95%CI: 0.15 to 1.54; p<0.001).

CONCLUSIONS: We found no conclusive evidence that multidomain interventions reduce the risk of global cognitive decline, symptoms of depression or apathy in a mixed older population. Our results suggest that these interventions may be more effective in those with lower baseline cognitive functioning. Extended follow-up for dementia occurrence is important to inform on the potential long-term effects of multidomain interventions.

Key words: Multidomain intervention trials, cognition, depression, apathy, pooled analysis.

Introduction

The global prevalence of dementia is expected to triple in the coming decades. Over 50 million individuals were living with dementia in 2019, and this number might rise to 152 million by 2050 (1). Around 30-40% of dementia cases might be attributable to potentially modifiable risk factors such as midlife hypertension, depression and physical inactivity (2–4). However, evidence from randomized controlled trials targeting these risk factors is inconsistent (5, 6).

Several large multidomain intervention studies using cognitive functioning or dementia as primary outcome have been performed in older persons from the general population free from dementia at baseline (7–9). Two major trials, the prevention of dementia by intensive vascular care trial (preDIVA) and Multidomain Alzheimer Preventive Trial (MAPT) reported no significant effect on their respective primary outcomes dementia and cognitive decline (10, 11). The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability trial (FINGER) is the only study so far which reported a modest excess improvement of cognitive functioning in the intervention group compared to an improvement in the control group (12).

Depression is a potentially modifiable risk factor for

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Table 1. Main characteristics of pooled trials

	preDIVA	MAPT
Country	the Netherlands	France
Duration	2006-2015	2008-2014
Sample size	3526	1679
Study design	open-label, cluster randomized controlled trial	placebo-controlled randomized superiority trial with four parallel groups
Inclusion site	116 general practices in 26 health-care center buildings	13 memory centers
Population	- age 70-78 - community-dwelling	- age 70+ - community-dwelling - spontaneous memory complaint, and/or limitation in activity of daily living, and/or slow gait speed
Intervention	nurse-led multidomain cardiovascular care (lifestyle advice supported by motivational interviewing techniques and drug treatment for hypertension, dyslipidaemia, and type 2 diabetes mellitus or antithrombotic drugs)	factorial design with two interventions: - multidomain intervention (cognitive training, physical activity, nutrition counseling, and three preventive consultations) - omega 3 supplement
Control	usual care	- usual care (vs. multidomain) - placebo (vs. omega-3)
Primary outcome	cumulative incidence of dementia	change in composite Z score combining four cognitive tests
Main secondary outcomes	cardiovascular events, mortality, change in cognitive function and depressive symptoms	cardiovascular events, functional assessment, depressive symptoms
Follow-up	6-8 years	3 years

dementia (3), and there is a bidirectional association between depression and cardiovascular risk factors and events (13-17). Apathy is associated with cardiovascular risk factors and increased risk of dementia (18, 19). A multidomain intervention targeting the same risk factors as those for dementia, could potentially reduce depressive symptoms and apathy. However, none of the trials reported significant effects of the interventions on symptoms of depression, and apathy was not reported.

Individual multidomain trials may have suffered from lack of power, due to the improvement in those in the control condition. In the preDIVA study, subgroup analyses suggested a potential beneficial effect in those with untreated hypertension, those with no history of cardiovascular disease at baseline, and in males (10). A more personalized approach, with interventions tailored to specific subgroups, could potentially lead to better intervention effects than a one-size-fits-all approach.

We pooled individual participant data from two large multidomain intervention trials targeting cardiovascular and lifestyle related risk factors to increase power and allow for subgroup analyses to detect possible intervention effects on cognition, symptoms of depression and apathy.

Methods

Study design and participants

We combined individual participant data from two large multidomain intervention trials targeting vascular and lifestyle-related risk factors in older people (10, 11). Both studies were European multicenter randomized controlled trials and included 3526 (preDIVA) and 1679 (MAPT) community dwelling individuals free from dementia at baseline, recruited from either general practices (preDIVA) or memory centers (MAPT). Individuals were aged 70 years or older and participants in MAPT were at increased risk for cognitive decline, operationalized as at least one of the three following criteria: spontaneous memory complaint expressed, limitation in one instrumental activity of daily living, or slow gait speed. The multidomain interventions consisted of individual or group sessions providing lifestyle advice concerning diet, physical activity and vascular risk factors. The MAPT study included cognitive training in the intervention. If needed, participants were advised to contact their general practitioner for optimization or initiation of drug treatment for cardiovascular risk factors. Control groups received usual care (10, 11). Main characteristics of the trials are specified in table 1. Study protocols have been published previously (20, 21). The MAPT study had a factorial design, with omega-3 supplementation in an additional arm (but there was no effect of this intervention on the trial's primary or secondary outcomes). In this analysis we only evaluate

Table 2. Baseline characteristics of the pooled sample

	All individuals N=4162 (100%)	Control N=1996 (48.0%)	Intervention N=2166 (52.0%)	P-value
Study				
- preDIVA	2818 (67.7)	1329 (66.6)	1489 (68.7)	
- MAPT	1344 (32.3)	667 (33.4)	677 (31.3)	
Demographics				
Age y, median (IQR)	74 (72-76)	74 (72-77)	74 (72, 76)	0.8
Female sex, n (%)	2403 (57.7)	1159 (58.1)	1244 (57.4)	0.7
Educational level, n (%)				
- Low	922 (22.4)	451 (23.0)	471 (21.9)	0.7
- Intermediate	2070 (50.3)	976 (49.7)	1094 (50.8)	
- High	1125 (27.3)	536 (27.3)	589 (27.3)	
Biological risk factors				
Systolic blood pressure (mmHg), mean (SD)	150.3 (21.6)	149.3 (20.9)	151.2 (22.1)	0.006
LDL cholesterol (mmol/L), mean (SD)	3.1 (1.0)	3.2 (1.0)	3.1 (1.0)	0.003
BMI (kg/m^2), mean (SD)	27.0 (4.2)	27.0 (4.1)	27.1 (4.2)	0.3

All individuals with at least one follow-up visit, and comparison of the intervention and control group. Differences between randomization groups in spite of the large numbers, may partly be due to cluster randomization in preDIVA. P-value for comparison between control and intervention. Abbreviations: BMI: Body Mass Index; IQR: interquartile range; LDL cholesterol: low-density lipoprotein cholesterol; SD: standard deviation

the multidomain intervention. The ethics committees in the respective medical centers approved both trials and all individuals gave written informed consent. Both trials were registered, respectively in the ISRCTN registry (preDIVA: ISRCTN29711771) and on ClinicalTrials.gov (MAPT: NCT00672685).

Outcomes

Global cognitive function was assessed with the Mini-Mental State Examination (MMSE). MMSE items were divided into anterograde episodic memory, evaluated with the delayed recall item (item 5, max 3 points) or 'other cognitive functions' (all other items). Both studies used different neuropsychological tests for memory (Visual Association Test (22) in preDIVA and Free and Cued Selective Reminding (23) in MAPT), precluding the possibility to use these more extensive memory tests in our analyses. As measure of subjective memory loss we used question 10 of the 15-item Geriatric Depression Scale (GDS-15): 'Do you feel you have more problems with memory than most?'. Depressive symptoms were quantified using the crude scores of the 15-item Geriatric Depression Scale (GDS-15) and using a dichotomized cut-off (GDS-15 >5: indicative of depression; ≤5: not indicative of depression). We additionally assessed the effect on apathy, operationalized as the three apathy items from the GDS-15 (GDS-3A), as has previously been shown to be an appropriate screening instrument for symptoms of apathy (24).

Statistical Analysis

We included participants with at least one follow-up visit to analyze the effect of the intervention on cognitive decline, symptoms of depression and apathy. Mean differences in change between the intervention and control group were calculated using linear mixed regression models. Crude continuous and binary scores were used as outcome, adjusted for baseline scores of the specific tests using analysis of covariance (ANCOVA). We used follow-up measures of the outcome of interest as outcome and treatment allocation as predictor, including random intercepts for participant and health center level. Model fit was estimated using Akaike Information Criterion values, and more complex models (i.e. with additional random slope for randomization allocation or the time difference between randomization and the follow-up visit) did not result in a better fit. Analyses were adjusted for the baseline measure of the outcome of interest, study, age, sex, time in study and also for LDL cholesterol and systolic blood pressure because of significant differences in baseline values between randomization groups. Furthermore, linear interaction for time in study was assessed by means of an interaction term. Predefined subgroup analyses were performed for 1) sex, since multidomain interventions may have differential effects in men and women, 2) baseline hypertension status defined as history of hypertension and/or systolic blood pressure of >140 mmHg, 3) history of myocardial infarction, stroke and/or diabetes at baseline, since there is a high probability that individuals with a history of cardiovascular disease already receive a

Table 3. Mean difference in effect of multidomain interventions on cognition, symptoms of depression and apathy after 3-4 years of follow-up

	Number of observations in analysis	Number of individuals in analysis	Baseline mean		Mean difference baseline and follow-up		Mean difference between intervention and control group
	N	N	Control	Intervention	Control	Intervention	MDc (95%CI)
Cognitive functioning							
MMSE (range 0-30)*	6677	3704	28.26	28.25	-0.09	-0.05	0.03 (-0.06 to 0.13)
Memory (MMSE item 5) (range 0-3)*	6774	3704	2.31	2.29	0.03	0.05	0.004 (-0.04 to 0.05)
Other (range 0-27)*	6677	3704	25.95	25.96	-0.12	-0.10	0.03 (-0.05 to 0.10)
Subjective memory loss (GDS15-Q10, % yes)†	6388	3503	18.15	19.53	0.03	-0.79	-0.51 (-2.52 to 1.50)
Depressive symptoms							
GDS (range 0-15)†	6279	3506	2.05	1.96	0.22	0.21	-0.04 (-0.16 to 0.07)
Depressive symptoms (% GDS >5)†	6279	3506	8.93	8.04	2.59	2.54	-0.68 (-2.32 to 0.97)
Apathy (range 0-3)†	6325	3503	0.70	0.69	0.12	0.12	-0.007 (-0.05 to 0.04)

* high score indicates better results; † low score indicates better results. Abbreviations: GDS: Geriatric Depression Scale; GDS15-Q10: question 10 of the Geriatric Depression Scale: 'Do you feel you have more problems with memory than most?'; MDc: mean difference in change between the intervention and control group; MMSE: Mini-Mental State Examination; 95%CI: 95% confidence interval

form of intervention and therefore, there might be more room for improvement in participants without a history of cardiovascular disease, 4) baseline MMSE <26, since individuals with lower baseline cognitive functioning might benefit more from a multidomain intervention, 5) educational level (low and high) because this is an important risk factor for dementia and is also associated with low socioeconomic status (3). Additional analyses were performed by study, to assess heterogeneity between the different studies. A p-value for interaction <0.05 was considered to reflect a significant interaction. Post-hoc analyses included exploration of differential dropout by comparing baseline characteristics of individuals included in the current study to individuals without any follow-up visits, and subgroup analyses for different cutoff values of baseline MMSE. Analyses were conducted in Rstudio (version 3.6.1, package "lme4") (25).

Results

Of a total of 5205 individuals in the two studies, 4162 (80%) individuals had at least one follow-up visit and were included in the present analysis (median follow-up duration: 3.7 years; IQR 3.0 to 4.14 years). The median age at baseline was 74 years (IQR 72, 76 years) and slightly more women were included (57.7%). No significant between-group differences in baseline characteristics were found in the pooled population, except for mean systolic blood pressure (control 149.3, SD 20.9; intervention 151.2, SD 22.1; p=0.006) and mean LDL cholesterol (control 3.19, SD 0.97; intervention 3.10, SD 0.95; p=0.003) (Table 2). eTable 1 shows baseline characteristics of included individuals per study. Participants who did not have a follow-up visit were slightly older, had a lower educational level, a slightly lower MMSE score, and a higher mean systolic blood pressure (eTable 2).

There were no differences in change from baseline to 3-4 year follow-up in MMSE and GDS scores between the control and intervention groups: Total MMSE score deteriorated by 0.09 points in the control group versus 0.05 points in the intervention group (mean difference in change [MDc] between intervention and control group: 0.03; 95% confidence interval [95%CI] -0.06 to 0.13). Total GDS score deteriorated by 0.21 points in the intervention group versus 0.22 points in the control group (MDc between intervention and control group: -0.04, 95%CI -0.16 to 0.07). The GDS-apathy score deteriorated by 0.12 points in both randomization groups (MDc between intervention and control group: -0.007 (-0.05 to 0.04). There was no time by treatment interaction for any of the outcome variables.

Subgroup Analysis

In individuals with a baseline MMSE score <26, total MMSE score improved over time in both randomization groups, but more in the intervention group (MDc 0.84 points, 95%CI 0.15 to 1.54). Similar effects were seen for anterograde episodic memory (MDc 0.21, 95%CI -0.01 to 0.43) and other MMSE items (MDc 0.74, 95%CI 0.26 to 1.21). In those with a baseline MMSE score ≥26, some deterioration or no change in MMSE scores (total, memory or other items) was seen with similar effects in both randomization groups (Table 5, eTable 3). No significant differences between randomization groups in change in test scores for cognitive functioning, depressive symptoms or apathy were found for sex, educational level, baseline hypertension status and history of cardiovascular disease or diabetes at baseline (Table 4, Table 5). In MAPT, stronger deterioration on other

Table 4. Mean difference in effect of multidomain interventions on cognition, symptoms of depression and apathy in subgroups (biological and clinical factors) after 3-4 years of follow-up

	Sex			Stroke, myocardial infarction or diabetes mellitus history			Hypertension		
	Male (n=1759) MDc (95%CI)	Female (n=2403) MDc (95%CI)	P for interaction	No (n=2739) MDc (95%CI)	Yes (n=1390) MDc (95%CI)	P for interaction	No (n=946) MDc (95%CI)	Yes (n=3216) MDc (95%CI)	P for interaction
Cognitive functioning									
MMSE (range 0-30)*	-0.02 (-0.17 to 0.12)	0.08 (-0.05 to 0.21)	0.30	0.08 (-0.04 to 0.20)	-0.04 (-0.22 to 0.13)	0.26	0.11 (-0.10 to 0.31)	-0.006 (-0.12 to 0.11)	0.28
Memory (MMSE item 5) (range 0-3)*	-0.04 (-0.11 to 0.02)	0.04 (-0.01 to 0.09)	0.05	0.02 (-0.03 to 0.08)	-0.04 (-0.11 to 0.04)	0.21	0.02 (-0.07 to 0.12)	-0.007 (-0.05 to 0.04)	0.49
Other (range 0-27)*	-0.006 (-0.12 to 0.11)	0.05 (-0.05 to 0.15)	0.46	0.05 (-0.04 to 0.15)	-0.009 (-0.15 to 0.13)	0.43	0.06 (-0.10 to 0.22)	0.003 (-0.09 to 0.09)	0.52
Subjective memory loss (GDS15-Q10, % yes)†	1.31 (-1.89 to 4.51)	-1.59 (-4.14 to 0.97)	0.15	-0.49 (-2.84 to 1.86)	-1.01 (-5.06 to 3.03)	0.91	-1.27 (-5.34 to 2.79)	-0.66 (-3.00 to 1.68)	0.71
Depressive symptoms									
GDS (range 0-15)†	-0.11 (-0.28 to 0.07)	-0.0004 (-0.15 to 0.15)	0.35	-0.06 (-0.20 to 0.08)	-0.06 (-0.27 to 0.15)	0.89	-0.04 (-0.31 to 0.24)	-0.07 (-0.20 to 0.05)	0.62
Depressive symptoms (% GDS >5)†	-0.01 (-0.03 to 0.01)	-0.002 (-0.02 to 0.02)	0.52	-0.008 (-0.03 to 0.01)	-0.009 (-0.04 to 0.02)	0.87	0.008 (-0.03 to 0.05)	-0.01 (-0.03 to 0.005)	0.22
Apathy (range 0-3)†	-0.04 (-0.11 to 0.03)	0.02 (-0.04 to 0.08)	0.22	-0.01 (-0.07 to 0.04)	0.01 (-0.08 to 0.10)	0.96	-0.05 (-0.16 to 0.05)	0.002 (-0.05 to 0.06)	0.44

The given numbers represent the number of individuals in the different subgroups in the full cohort. These numbers slightly differed in each analysis. * high score indicates better results; † low score indicates better results. Abbreviations: GDS: Geriatric Depression Scale; GDS15-Q10: question 10 of the Geriatric Depression Scale: 'Do you feel you have more problems with memory than most?'; MDc: mean difference in change between the intervention and control group; MMSE: Mini-Mental State Examination; 95%CI: 95% confidence interval

Table 5. Mean difference in effect of multidomain interventions on cognition, symptoms of depression and apathy in subgroups (baseline cognition and educational level) after 3-4 years of follow-up

	Baseline MMSE			Educational level		
	<26 (n=296) MDc (95%CI)	≥26 (n=3866) MDc (95%CI)	P for interaction	Low (n=922) MDc (95%CI)	High (n=3240) MDc (95%CI)	P for interaction
Cognitive functioning						
MMSE (range 0-30)*	0.84 (0.15 to 1.54)	-0.03 (-0.12 to 0.06)	<0.001	0.13 (-0.11 to 0.37)	-0.002 (-0.10 to 0.10)	0.23
Memory (MMSE item 5) (range 0-3)*	0.21 (-0.01 to 0.43)	-0.01 (-0.05 to 0.03)	0.008	0.02 (-0.08 to 0.11)	0.0008 (-0.05 to 0.05)	0.68
MMSE other (range 0-27)*	0.74 (0.26 to 1.21)	-0.02 (-0.09 to 0.05)	<0.001	0.07 (-0.13 to 0.27)	-0.002 (-0.08 to 0.08)	0.32
Subjective memory loss (GDS15-Q10, % yes)†	-1.83 (-10.86 to 7.21)	-0.37 (-2.42 to 1.67)	0.81	-2.32 (-7.00 to 2.37)	0.13 (-2.07 to 2.34)	0.41
Depressive symptoms						
GDS (range 0-15)†	-0.17 (-0.66 to 0.32)	-0.04 (-0.16 to 0.08)	0.74	0.05 (-0.22 to 0.32)	-0.06 (-0.19 to 0.06)	0.43
Depressive symptoms (% GDS >5)†	-0.06 (-0.14 to 0.02)	-0.003 (-0.02 to 0.01)	0.099	0.01 (-0.03 to 0.05)	-0.009 (-0.03 to 0.008)	0.39
Apathy (range 0-3)†	0.03 (-0.16 to 0.21)	-0.01 (-0.06 to 0.04)	0.58	0.003 (-0.10 to 0.11)	-0.005 (-0.06 to 0.05)	0.86

The given numbers represent the number of individuals in the different subgroups in the full cohort. These numbers slightly differed in each analysis. * high score indicates better results; † low score indicates better results. Abbreviations: GDS: Geriatric Depression Scale; GDS15-Q10: question 10 of the Geriatric Depression Scale: 'Do you feel you have more problems with memory than most?'; MDc: mean difference in change between the intervention and control group; MMSE: Mini-Mental State Examination; 95%CI: 95% confidence interval

MMSE items was seen in the control group compared to the intervention group, but there was no effect in preDIVA. None of the other outcomes were significantly different between both studies (eTable 4).

To assess the consistency of the effects favoring the intervention in individuals with a low baseline MMSE, we performed post-hoc subgroup analyses stratified for various baseline MMSE cutoff scores (eTable 5). The highest MDc were found with a baseline MMSE cut-off score <26, and with increasing baseline MMSE scores, MDc between the intervention and control group gradually decreased. Individuals with MMSE score <26 at baseline were significantly lower educated and had a higher Body Mass Index at baseline (eTable 6). Additional adjustment for these covariates did not significantly change the MDc between the intervention and control group in total MMSE score (baseline MMSE ≤26: MMSE MDc 0.77, 95%CI 0.07 to 1.47; p<0.001). There was no differential dropout between both randomization groups in individuals with a baseline MMSE score <26 and > 26 points.

Discussion

This pooled analysis of two large randomized controlled trials in community-dwelling individuals over 60 years old did not show an overall effect of multidomain interventions on cognitive function or symptoms of depression or apathy after 3-4 years follow-up. Subgroup analyses suggests that multidomain interventions may improve cognition in those with lower cognitive scores at baseline. We observed no interaction of the effect of the interventions with sex, history of stroke, diabetes mellitus and/or myocardial infarction, hypertension and educational level.

Strengths and limitations

The major strength of this study is that we pooled data on individual participant level from two large randomized controlled trials, providing more power to detect possible intervention effects on cognition, symptoms of depression and apathy, and to better allow for subgroup analyses to explore whether interventions may be more effective in specific subgroups. Furthermore, variation in inclusion criteria and multidomain interventions between the different trials improved the external validity of our overall results.

Several limitations should be noted. First of all, the use of the MMSE as outcome measure for cognitive studies has limitations. This time-honored test was designed as a cognitive screening test and does not measure cognitive function as comprehensively or sensitively, or with such detailed quantification, as a full neuropsychological evaluation does. Assessments using cognitive screening instruments such as the MMSE are known to show substantial variation over time, depending on conditions such as e.g. illness, stress or sleep deprivation, particularly in people without cognitive impairments (26), although the same holds for full neuropsychological evaluation. A possible random error caused by these fluctuations may have resulted in bias towards the null. Another disadvantage of the MMSE in populations such as under study here, is its ceiling effect. It lacks the ability to differentiate well between healthy individuals and early signs of dementia in individuals with MMSE scores in the range of 24-30. However, despite its limitations, as with any other screening test, the MMSE is characterized by an unprecedented dissemination and appreciation among the scientific epidemiological and dementia community. Moreover, these interventions were not designed to boost cognition, but to prevent cognitive decline. Less decline in MMSE was a more likely hypothesis than more increment in MMSE due to the intervention – nuancing the potential ceiling effect. Secondly, attrition bias could have influenced our results, since those who dropped out were significantly older, had a lower educational level, higher mean systolic blood pressure, and lower MMSE scores; i.e. they were at higher risk of cognitive decline. This could have biased our results to the null, since those with lower cognitive function appear to potentially benefit most from intervention. Lastly, while both studies were designed to test the efficacy of multidomain interventions in elderly, there were important differences in study design and populations between both trials which could have impacted the results of this study. The recruitment strategy of individuals in preDIVA was population-based through general practices, whereas MAPT recruited individuals at risk for cognitive decline through memory centers. Cognitive training was not part of the intervention in preDIVA, but the intervention in MAPT strongly focused on cognitive training in the intervention group, which was given in supervised sessions, in contrast to the physical activity and nutrition components which were simply based on advice. Moreover, cardiovascular risk factors in the intervention group in preDIVA were assessed every four months by a practice nurse, and if necessary, medical interventions such as drug treatment were advised according to a detailed protocol. The MAPT intervention assessed cardiovascular risk factors annually, and there was less focus on drug treatment. These differences might improve the external validity of our results, but they are likely to also cause heterogeneity. However, there were no structural differences in intervention effects between the MAPT and preDIVA intervention.

Although overall this study did not show beneficial effects of multidomain interventions on symptoms of depression and apathy and cognitive function, several methodological challenges associated with dementia prevention trials complicate the interpretation of these results. First, the development of cognitive impairment and dementia is a slow and insidious process, and risk factors in midlife have a stronger association with

incident dementia than risk factors in later life (27–30). However, since inclusion of participants in midlife requires an unrealistically long follow-up (31), these trials included participants in later life, far beyond the stage of life in which interventions are expected to have their optimal effect. Second, follow-up durations for the current analyses were too short to detect an effect on incident dementia, as most clear clinically relevant outcome. Long-term interventions starting at a younger age might be needed to achieve clinically relevant effects.

Although observational studies have shown consistent evidence supporting the association of cardiovascular risk factors and lifestyle related factors with cognitive decline and dementia, and some interventions targeting these factors have shown to improve cognitive function (3, 4, 32), trials evaluating multidomain interventions report inconsistent results (10–12, 33). Variation in intensity, components of the multidomain intervention, and characteristics of the control condition in the individual trials may partly explain these inconsistent results. Alternative explanations include that the associations found in observational studies do not reflect a causal relationship or that the harmful effects have been effectuated by the time these interventions started.

Subgroup analyses for individuals with low baseline MMSE score yielded consistent results with beneficial effects of the multidomain intervention on cognitive function: total MMSE score, including anterograde episodic memory and other MMSE items increased more in the intervention group. Similar effects on memory were seen in a multidomain intervention trial in black individuals with MCI (34). The size of these groups (MMSE <26) was small within the overall studies (n=296). However, the gradual decrease in MDc with increasing baseline MMSE score appeared to be consistent (Table 4), and the results did not change with additional adjustment for differences in baseline characteristics. Furthermore, results were still statistically significant after multiple-comparison correction ($p < 0.01$ after Bonferroni correction). These findings should be confirmed in the multidomain intervention trials that are currently underway (35–37).

The underlying etiology of dementia is heterogeneous, and a multidomain intervention tailored to specific subgroups could potentially lead to better intervention effects than a one-size-fits-all approach. The results of this study, showing that, in later life, this type of intervention may be more effective in those with lower baseline cognitive scores, should be considered in the design of future dementia prevention trials.

Conclusion

This study with pooled data at the individual participant level from two large, randomized controlled trials did not show conclusive evidence that multidomain interventions can reduce the risk of cognitive decline or symptoms of depression and apathy in a mixed older population. These interventions may be more effective in those with lower baseline cognitive function. Extended follow-up for dementia outcomes is important to evaluate whether multidomain interventions can indeed have beneficial effects crossing the threshold of minimal clinically important difference. These extended follow-ups are planned and ongoing in both trials.

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