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Multidomain interventions for preventing cognitive decline in older adults with type 2 diabetes and mild cognitive impairment: Secondary analysis of the J-MINT
Multidomain intervention in type 2 diabetes

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ABSTRACT

Aims: To identify subgroups who may be more likely to respond well to a multidomain intervention among older adults with type 2 diabetes.
Materials and methods: This study was a secondary analysis of the Japan Multimodal Intervention Trial for Prevention of Dementia. A total 531 participants aged 65–85 years with mild cognitive impairment were randomized into intervention (vascular risk management, exercise, nutritional counseling, and cognitive training) and control (health-related information) groups. The outcome was the change in average Z scores of neuropsychological tests from baseline to 18 months. Interactions between intervention and age (65–74, 75–85 years), memory impairment (amnestic, nonamnestic), HbA1c levels (within, outside target range), or *APOE* genotype (0, ≥1 *APOE* ϵ4 alleles) among participants with diabetes were evaluated using the mixed-effects model for repeated measures.
Results: Among 76 participants with diabetes, a significant age × intervention interaction ($P = 0.007$) was found, which was driven by benefits in the younger age group (Z score difference: 0.33, 95% CI: 0.09 to 0.55) that were not observed in the older age group. Intervention benefits were also detected in those with HbA1c levels outside the target range (Z score difference: 0.31, 95% CI: 0.06 to 0.56), with HbA1c levels × intervention interaction ($P = 0.021$). No significant interactions were detected between intervention and memory impairment or *APOE* genotype.
Conclusions: Multidomain interventions may benefit younger older adults or those with overly strict or lenient HbA1c control; however, these findings need confirmation in future studies.

1. Introduction

Diabetes increases the risk of developing dementia, including vascular dementia and Alzheimer's disease [1]. Although the underlying mechanisms of cognitive impairment in diabetes remain unclear, several potentially modifiable factors such as hyperglycemia [2], severe hypoglycemia [3], glycemic variability [4], physical activity [5], nutritional status [6], diet [7], and social engagement [8], have been considered

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possible mechanisms driving the risk for cognitive decline and dementia in people with diabetes. Multidomain intervention trials targeting at-risk individuals or those with mild cognitive impairment (MCI) have been conducted to address these factors and mechanisms simultaneously [9]. However, the results have been inconsistent [10]. Recently, several studies have reported positive effects [11–14], whereas others have reported nonsignificant results [15,16].

The Japan-Multidomain Intervention Trial for Prevention of Dementia in Older Adults with Diabetes (J-MIND-Diabetes), an 18-month, randomized controlled trial, failed to demonstrate the efficacy of a multidomain intervention (management of vascular risk factors, exercise, dietary counselling, and promotion of social participation) in the primary endpoints, specifically changes in composite cognition scores, among 154 older adults with type 2 diabetes and MCI [17]. The study was significantly impacted by the coronavirus disease 2019, facing multiple challenges, including failure to reach the target sample size. Despite these limitations, secondary analyses revealed a positive impact on memory function, along with evidence of dietary behavioral changes and weight reduction [17]. These findings showed proof of-concept for multidomain interventions in this population. Furthermore, exploratory analyses from the Look AHEAD study showed that multidomain lifestyle interventions in people with diabetes and obesity had beneficial effects on white matter hyperintensities, ventricle volumes, and cerebral blood flow [18,19], although there was no significant effect on cognitive decline [20]. However, there is still a lack of evidence on the efficacy of multidomain interventions among older adults with diabetes. Furthermore, it remains unclear whether there may be target populations who exhibit greater responsiveness to multidomain interventions among people with diabetes, although trials in the general population suggest that relatively young study populations and older adults with a genetic high risk for dementia, specifically those carrying *APOE* $\varepsilon 4$ alleles closely associated with Alzheimer's disease, are more likely to benefit from multidomain interventions [10].

This secondary analysis of the Japan Multimodal Intervention Trial for Prevention of Dementia (J-MINT) [16] aimed to investigate the efficacy of multidomain interventions in preventing cognitive decline and identify particular subgroups who may be more likely to respond well to these interventions among older adults with type 2 diabetes. Based on previous research, age, *APOE* status, and memory impairment—factors closely associated with Alzheimer's disease—were selected as key factors for subgroup analysis [10]. In addition, glycemic control status—categorized as within the target range, above the target range (leniently controlled), or below the target range (strictly controlled), was selected, considering its association with risk for incident dementia in older adults with diabetes [21].

2. Materials and Methods

2.1. Study population and design

Data for these subgroup analyses were obtained from the J-MINT trial, an 18-month, randomized, controlled, multicenter study conducted at five independent institutes in Japan. The study protocol and primary findings have been previously published [16,22]. The J-MINT recruited 531 participants aged 65–85 years who had age- and education-adjusted cognitive decline from hospitals, memory clinics, and/or community-based cohorts. Participants who had been diagnosed with dementia or who had a Mini-Mental State Examination (MMSE) score of <24 were excluded [23]. All participants received a comprehensive explanation of the trial's objectives and potential risks before providing written informed consent. The study protocol was reviewed and approved by the Institutional Review Boards of all participating institutions.

Among the 531 participants, those who attended at least one session of the intervention program or general health instruction and completed at least one post-baseline neuropsychological assessment were included in the secondary analysis.

2.2. Randomization and masking

Participants were randomly assigned in a 1:1 ratio to either the intervention or control group using a dynamic allocation method, stratified by age at enrollment (65–74 vs. 75–85 years), sex (female vs. male), MMSE score (24–27 vs. 28–30), and memory impairment status (amnestic vs. nonamnestic). Research staff responsible for evaluating the primary outcome data were blinded to group assignments and were not involved in delivering the intervention. However, staff administering the intervention and the participants themselves were aware of group allocation [22].

2.3. Interventions

In vascular risk management, results of blood tests and brain MRI or CT scans were mailed to all participants, accompanied by letters advising them to consult their primary healthcare providers if necessary. Additionally, participants in the control group received general health-related information in writing every 2 months [22].

The intervention group received further multidomain intervention programs, which included group-based physical exercise, nutritional counseling, and cognitive training [22]. Group-based physical exercise sessions were conducted once a week, lasting 90 minutes, and included stretching, strength training, aerobic exercise, dual-task training, and group discussions. A total of 78 sessions were held throughout the intervention period. Nutritional counseling sessions were individually provided by qualified health consultants. During the intervention period, three 60-min face-to-face counseling sessions and 12 telephone counseling sessions were provided. Participants were encouraged to engage in cognitive training individually using the Brain HQ (Posit Science Corporation, San Francisco, CA), which was customized for the J-MINT trial. During the 18-month intervention period, three intensive training phases were implemented, each lasting 3 months. Participants were instructed to engage in cognitive training for at least 30 min per day, ≥4 days per week [22].

2.4. Type 2 diabetes and glycemic control status

Participants diagnosed with type 2 diabetes, those receiving diabetes medications, or those with HbA1c levels ≥6.5% were classified as having type 2 diabetes. Based on the glycemic targets set by the Japan Diabetes Society (JDS)/Japan Geriatrics Society (JGS) Joint Committee [24], glycemic control status was classified into the following three groups: within the target range, above the target range, and below the target range. In older adults with diabetes, an HbA1c target of <7.0% is generally recommended. However, the JDS/JGS guidelines emphasized individualized glycemic goals based on a patient's overall health status. In individuals with cognitive impairment, less stringent targets may be considered, and a lower limit is applied when they are receiving medications associated with a higher risk for severe hypoglycemia (i.e., sulfonylureas, glinides) to minimize the risk of hypoglycemic events. In the present study, for participants not receiving these drugs, the target for HbA1c levels was determined as <7.0% without a lower limit, and for those receiving these drugs, the target HbA1c range was 7.0%–7.9% [24].

2.5. Outcomes

The primary outcome of this analysis was the change in average Z scores from baseline to the 18-month follow-up. This score was derived from multiple neuropsychological assessments, including the MMSE [23], the Logical Memory I and II subset of the Wechsler Memory Scale-Revised [25], the Free and Cued Selective Reminding Test (FCSRT) [26],

the Digit Span of the Wechsler Adult Intelligence Scale (WAIS)-III [27], the Trail Making Test (TMT) [28], the Digit Symbol Substitution Test (DSST) subset of WAIS-III [27], and the letter fluency test [28]. The Z scores of each neuropsychological test were standardized with baseline mean and standard deviation values for each test from all participants included in this secondary analysis. For TMT, inverse Z scores were used because lower scores indicate better cognitive function.

Furthermore, based on procedures outlined in a previous study [29], domain composite scores were calculated as secondary outcomes. An expert panel consisting of neuropsychologists and statisticians assigned items from the cognitive tests to one of the following domains: memory (MMSE time and place orientation and 3-word immediate and delayed recall, logical memory immediate and delayed recall for story A and B), language (letter fluency test, MMSE repetition, command, and reading), executive functioning (TMT part A and B, DSST, digit span forward and backward tests, MMSE serial 7's), and visuospatial functioning (MMSE copy pentagon). Data quality control was conducted after the domain assignment. The statisticians modeled each domain separately using the confirmatory factor analysis in Mplus. Due to low inter-test correlations (letter fluency test and MMSE repetition, $r = 0.02$; letter fluency test and MMSE reading, $r = 0.02$; MMSE repetition and command, $r = 0.01$), which resulted in language domain scores being estimated with higher standard errors, the language score was excluded from further analysis. In addition, because visuospatial functioning was evaluated using only one item, the MMSE pentagon copying task, a composite score for visuospatial functioning could not be calculated. Therefore, the domain scores for memory and executive functioning were used as secondary outcome variables in the analysis.

2.6. Other variables

At baseline, participant characteristics such as age, sex, education, medications, and self-reported comorbidities, including diabetes and diabetes duration, hypertension, and dyslipidemia, were evaluated using a self-reported questionnaire. Height and weight were measured and used for calculating body mass index. HbA1c levels and *APOE* genotype were evaluated.

2.7. Statistical methods

Categorical variables were presented as frequencies and percentages, whereas continuous variables were summarized as means and standard deviations. Baseline characteristics of participants with and without diabetes were compared using the Kruskal–Wallis or χ^2-tests. The mixed-effects model for repeated measures (MMRM) was used for determining the efficacy of multidomain interventions in preventing cognitive decline among participants with and without type 2 diabetes [30]. The outcomes were the average Z scores and cognitive domain composite scores, and the regression model included covariates for age at randomization (65–74 and 75–85 years), sex, years of education, presence of memory impairment at randomization, baseline cognitive score, and all 2-way and 3-way interaction terms between intervention allocation, presence of diabetes, and time visit. The unstructured covariance structure was adopted, and the Kenward–Roger adjustment method [31] was used to calculate CIs and *P* values.

To evaluate the effect modifications that possibly indicate more beneficial effects from the multidomain interventions in participants with type 2 diabetes, we conducted MMRM analyses incorporating all 2-way and 3-way interaction terms between intervention allocation, time visit, and subgroups based on age at enrollment (65–74 vs. 75–85 years), presence of memory impairment (amnestic vs. nonamnestic), HbA1c levels according to the JDS/JGS-recommended target range (within vs. above/below the target range), and *APOE* genotype (0 vs. ≥1 *APOE* ε4 alleles), adjusting the same covariates using the abovementioned model.

All statistical analyses were conducted using Stata 17.0 (Stata Corp.) and R ver. 4.3.2 (R Foundation for Statistical Computing). All *P* values were two-tailed, and significance levels were set at $\alpha = 0.05$. For interaction tests between intervention and subgroups in participants with type 2 diabetes, the Benjamini–Hochberg procedure was applied with controlling the false discovery rate at 0.05 to address the issue of multiplicity [32].

3. Results

3.1. Participant characteristics

Of the 531 participants in the J-MINT, 81 withdrew after randomization, and 17 had no evaluations after baseline, resulting in 433 participants for inclusion in this analysis (Supplementary Figure 1). Of these 433 participants, 76 had type 2 diabetes. Table 1 shows the baseline characteristics of the participants. Participants with diabetes were more likely to be male and to have dyslipidemia, higher HbA1c levels, and lower cognitive function on TMT part A ($P < 0.05$). Participants with diabetes were less likely to have ≥1 *APOE* ε4 alleles than those without type 2 diabetes ($P = 0.047$). Supplementary Tables 1–5 present the raw scores for all cognitive tests at baseline and follow-up, stratified by diabetes status and other subgroups.

3.2. Intervention effects on cognitive outcomes

In the MMRM analyses, no significant intervention effects were found on changes in the average Z score between the intervention and control groups in the entire group of participants with diabetes (difference in Z score = 0.08, 95% CI = −0.11 to 0.27, $P = 0.395$) or the entire group of participants without diabetes (difference in Z score = 0.04, 95% CI = −0.05 to 0.12, $P = 0.377$) (P for interaction = 0.682) (Table 2).

In the interaction analyses among participants with type 2 diabetes, the interaction between intervention and age groups was significant (P for interaction = 0.007), which remained significant even when applying the Benjamini–Hochberg procedure (P for interaction = 0.028). This difference appeared to be driven by the intervention benefit in the younger group (n = 31, difference in Z score = 0.33, 95% CI = 0.09 to 0.55, $P = 0.007$, Figure 1A), which was not observed in the older group (n = 45, difference in Z score = −0.10, 95% CI = −0.29 to 0.09, $P = 0.300$, Figure 1B). Similarly, when the HbA1c target ranges were considered, a significant interaction was detected between the intervention and glycemic control groups (P for interaction = 0.021), which remained significant even when applying the Benjamini–Hochberg procedure (adjusted P for interaction = 0.042). The difference appeared to be driven by the intervention benefit in the group with HbA1c levels outside the target range (n = 32, difference in Z score = 0.31, 95% CI = 0.06 to 0.56, $P = 0.015$, Figure 2B), which was not observed in the group with HbA1c levels within the target range (n = 44, difference in Z score = −0.07, 95% CI = −0.27 to 0.13, $P = 0.490$, Figure 2A). There were no significant interactions between intervention and memory impairment or the *APOE* genotype (Table 2).

When each cognitive domain score was analyzed, for the memory score, there was an interaction between intervention and age group (P for interaction = 0.022); however, it did not remain significant when applying the Benjamini–Hochberg procedure (adjusted P for interaction = 0.088). The difference appeared to be driven by the intervention benefit in the younger group (n = 31, difference in memory score = 0.37, 95% CI = 0.05 to 0.68, $P = 0.023$), which was not observed in the older group (n = 41, difference in memory score = −0.12, 95% CI = −0.38 to 0.48, $P = 0.273$) (Supplemental Table 6). For the executive functioning score, no significant interaction was detected between intervention and subgroups.

4. Discussion

This secondary analysis of the J-MINT investigated the efficacy of multidomain interventions in preventing cognitive decline in older

Table 1
Baseline characteristics of the participants with and without type 2 diabetes.

	With diabetes (n = 76)		Without diabetes (n = 357)		With diabetes vs. without diabetes
	Intervention group (n = 35)	Control group (n = 41)	Intervention group (n = 180)	Control group (n = 177)	*P*
Sex, Female	15 (42.9)	16 (39.0)	97 (53.9)	98 (55.4))	0.028
Age, years	75.1 (5.5)	75.0 (4.5)	74.2 (4.9)	74.3 (4.8)	0.171
Education, years	12.6 (2.9)	12.7 (2.7)	12.6 (2.5)	12.5 (2.3)	0.674
Body mass index, kg/m^2	24.0 (2.7)	23.2 (3.7)	23.1 (3.5)	22.8 (3.4)	0.151
Self-reported comorbidities					
Hypertension	21 (60.0)	20 (48.8)	79 (43.9)	80 (45.2)	0.135
Dyslipidemia	23 (65.7)	20 (48.8)	57 (31.7)	57 (32.2)	<0.001
Presence of memory impairment	16 (45.7)	19 (46.3)	69 (38.3)	66 (37.3)	0.182
HbA1c, %	6.9 (0.8)	6.9 (1.0)	5.5 (0.3)	5.5 (0.3)	<0.001
Glycemic control status					
Within the target range	20 (57.1)	24 (58.5)	–	–	–
Above the upper limit	8 (22.9)	13 (31.7)	–	–	–
Below the lower limit	7 (20.0)	4 (9.8)	–	–	–
Duration of diabetes*, years	16.1 (11.7)	13.3 (10.9)	–	–	–
Medications for diabetes treatment	26 (74.3)	30 (73.2)	–	–	–
Insulin	0 (0.0)	0 (0.0)	–	–	–
Sulfonylurea	8 (22.9)	4 (9.8)	–	–	–
Glinides	5 (14.3)	5 (12.2)	–	–	–
Biguanides	15 (42.9)	14 (34.2)	–	–	–
α–glucosidase inhibitors	7 (20.0)	5 (12.2)	–	–	–
Thiazolidinediones	1 (2.9)	3 (7.3)	–	–	–
Dipeptidyl peptidase 4 inhibitors	22 (62.9)	24 (58.5)	–	–	–
Glucagon-like peptide 1 receptor agonists	0 (0.0)	0 (0.0)	–	–	–
Sodium-glucose cotransporter 2 inhibitors	7 (20.0)	5 (12.2)	–	–	–
≥1 *APOE* ε4 alleles*	7 (20.0)	8 (19.5)	63 (35.6)	46 (26.6)	0.047
Neuropsychological test*					
Average Z scores	–0.1 (0.6)	0.0 (0.5)	–0.0 (0.6)	0.1 (0.6)	0.357
Domain composite score, executive function	–0.1 (0.8)	0.2 (0.7)	0.0 (0.8)	0.1 (0.9)	0.818
Domain composite score, memory	0.2 (0.7)	–0.0 (0.7)	0.1 (0.7)	0.2 (0.7)	0.490
MMSE	27.6 (2.4)	27.6 (1.9)	27.8 (1.8)	27.6 (1.8)	0.581
FCSRT	45.6 (5.3)	44.8 (4.0)	44.4 (6.7)	44.8 (5.6)	0.432
Logical memory					
Immediate recall	18.1 (6.9)	15.5 (7.2)	16.6 (7.6)	17.8 (7.6)	0.661
Delayed recall	12.8 (7.8)	10.2 (8.0)	11.3 (7.7)	12.2 (7.7)	0.739
Digit symbol substitution test	48.1 (15.1)	53.3 (15.2)	54.1 (14.0)	55 (16.2)	0.066
Trail Making Test					
Part A	67.3 (28.5)	64.6 (29.9)	58.6 (24.9)	59.9 (26.5)	0.049
Part B	141.3 (75.8)	120.2 (70.5)	117.5 (58.5)	115.4 (61.8)	0.090
Digit span					
Forward	8.2 (1.9)	8.5 (2.0)	8.1 (1.8)	8.2 (2.0)	0.384
Backward	5.1 (1.7)	5.3 (1.7)	5.2 (1.6)	5.3 (1.8)	0.833
Letter word fluency test	9.3 (3.5)	9.1 (3.9)	9.4 (3.4)	9.3 (3.2)	0.623

Data are presented as n (%), n/N (%), or mean (SD). *Data not available for all randomized participants.
The glycemic target range was HbA1c <7.0% without a lower limit for participants not receiving drugs potentially associated with severe hypoglycemia (insulin, sulfonylurea, or glinides) and 7.0%–7.9% for those receiving these drugs.
APOE, apolipoprotein E; FCSRT, Free and Cued Selective Reminding Test; MMSE, Mini-Mental State Examination; SD, standard deviation.

adults with and without type 2 diabetes. The multidomain interventions did not exert significant efficacy in preventing cognitive decline in participants with or without type 2 diabetes. However, further analyses focusing on participants with type 2 diabetes suggested that multidomain interventions may be particularly valuable for younger older adults (age 65–74 years) or those with HbA1c levels outside the target range, including both overly strict and lenient control. Nonetheless, this finding should be confirmed with additional datasets and larger trials with prespecified hypotheses.

Consistent with our findings, previous multidomain intervention trials also did not demonstrate significant effects on cognitive functions in older adults with type 2 diabetes [17,18]. It remains unclear whether there are target populations who may exhibit greater responsiveness to such interventions. In the present study, participants with diabetes aged 65–74 years in the intervention group exhibited improved cognitive function, particularly in memory, with a significant interaction between the intervention and age group. This finding suggests that relatively younger individuals with diabetes may benefit more from multidomain interventions, supporting the recommendations, emphasized in a previous review, that risk reduction interventions should preferably start early, before substantial brain pathology and cognitive impairment have already occurred [33]. In contrast, cognitive function tended to decline among participants aged 75–85 years irrespective of intervention group allocation (Figure 1B). Although the reasons for this difference in response to interventions between age groups are unclear, participants with diabetes aged 75–85 years had lower baseline cognitive function and lower adherence to cognitive training sessions than younger participants aged 65–74 years, whereas metabolic control and duration of diabetes were not different (Supplementary Table 7). Considering that adherence is one of the most important factors in achieving the benefits of multidomain interventions [16,34], lower adherence may contribute to lower intervention benefits in older adults aged 75–85 years. Nevertheless, in a recent trial, cognitive improvements were observed in individuals aged even >70 years with at least two dementia risk factors, which include poor diabetes management, following a 2-year personalized risk reduction intervention [11]. These results and our findings

Table 2
Estimated mean difference in the change in the average Z scores from baseline to the 18-month follow-up among participants with and without type 2 diabetes.

	Estimated mean changes from baseline to 18-month follow-up				Interaction	
	Intervention group	Control group	Mean differences between randomization groups	*P*	Coefficient (SE)	*P*
Overall participants (n = 433)						
Presence of type 2 diabetes						
With type 2 diabetes (n = 76)	–0.020 (–0.157 to 0.117)	–0.100 (–0.226 to 0.025)	0.080 (–0.105 to 0.266)	0.395	0.043 (0.103)	0.682
Without type 2 diabetes (n = 357)	0.048 (–0.012 to 0.107)	0.010 (–0.051 to 0.070)	0.038 (–0.046 to 0.122)	0.377		
Participants with type 2 diabetes (n = 76)						
Age at enrollment						
65–74 years (n = 31)	0.235 (0.065 to 0.406)	–0.087 (–0.245 to 0.071)	0.332 (0.092 to 0.553)	0.007	0.424 (0.150)	0.007*
75–85 years (n = 45)	–0.213 (–0.358 to –0.068)	–0.111 (–0.243 to 0.022)	–0.102 (–0.294 to 0.091)	0.300		
Presence of memory impairment						
Without memory impairment (n = 41)	0.026 (–0.140 to 0.191)	–0.066 (–0.221 to 0.089)	0.091 (–0.133 to 0.316)	0.419	0.038 (0.161)	0.813
With memory impairment (n = 35)	–0.069 (–0.246 to 0.109)	–0.121 (–0.277 to 0.034)	0.053 (–0.177 to 0.283)	0.647		
HbA1c levels relation to JDS/JGS glycemic targets						
Within the target range (n = 44)	–0.063 (–0.220 to 0.093)	0.007 (–0.132 to 0.145)	–0.070 (–0.272 to 0.132)	0.490	–0.382 (0.161)	0.021*
Above or below the target range (n = 32)	0.049 (–0.132 to 0.230)	–0.263 (–0.439 to –0.087)	0.312 (0.062 to 0.562)	0.015		
APOE status						
0 *APOE* ε4 allele (n = 61)	–0.016 (–0.148 to 0.117)	–0.085 (–0.208 to 0.039)	0.069 (–0.110 to 0.248)	0.444	–0.026 (0.204)	0.901
≥1 *APOE* ε4 alleles (n = 15)	–0.040 (–0.321 to 0.241)	–0.135 (–0.375 to 0.105)	0.094 (–0.269 to 0.458)	0.605		

The glycemic target range was HbA1c <7.0% without a lower limit for participants not receiving drugs potentially associated with severe hypoglycemia (insulin, sulfonylurea, or glinides) and 7.0%–7.9% for those receiving these drugs.
APOE, apolipoprotein E; JDS/JGS, Japan Diabetes Society / Japan Geriatrics Society; MMSE, Mini-Mental State Examination; SE, standard error.
*: Remained statistically significant after Benjamini-Hochberg false discovery rate 0.05 correction.

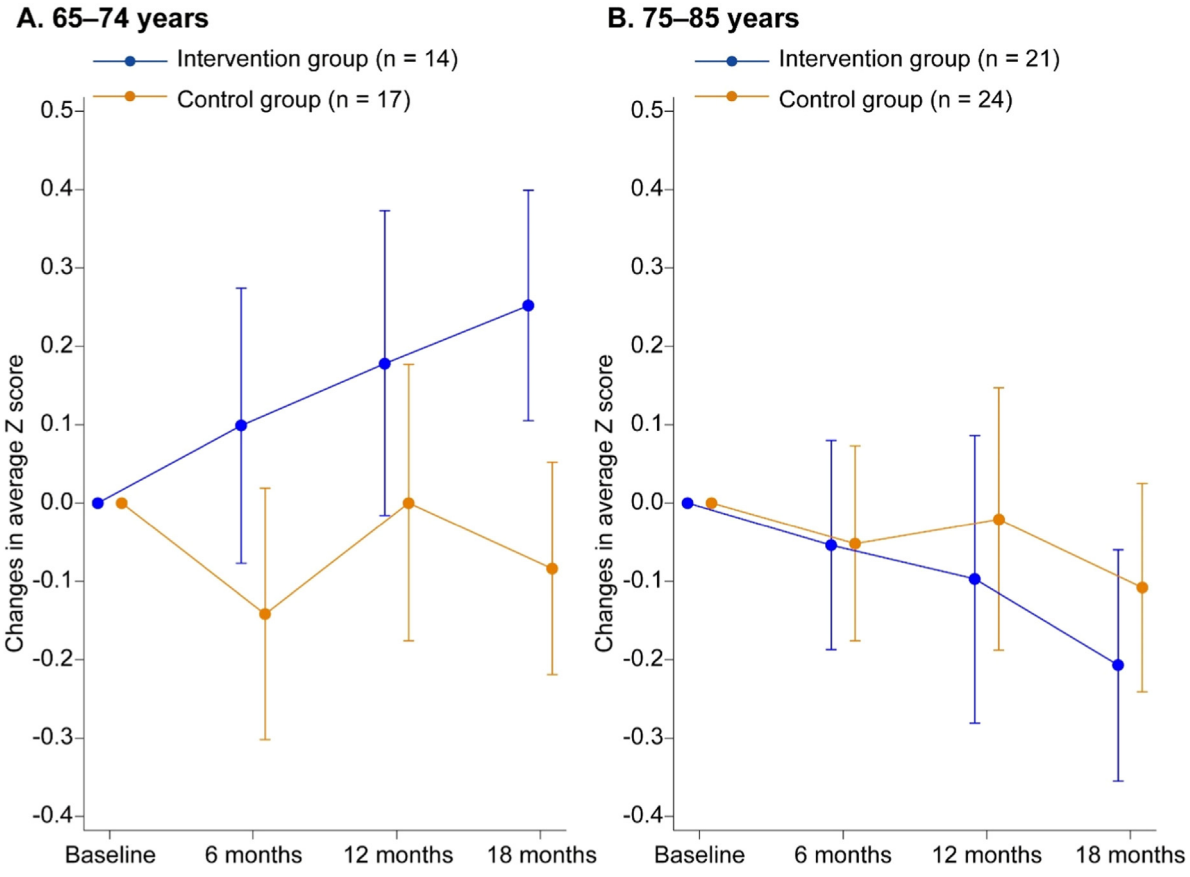

Figure 1. Changes in the average Z score from baseline to 18-month follow up according to age at enrollment in participants with type 2 diabetes.

suggest that personalized or tailored interventions, including support for improving adherence, are essential to maximize the effectiveness of multidomain interventions among older adults in the later stages of life. In this context, future studies may benefit from employing innovative methodologies, such as Bayesian adaptive trial designs or n-of-1 trials, which offer more flexible and individualized approaches for evaluating intervention efficacy in heterogeneous aging populations.

The present study suggested that individuals with HbA1c levels outside the glycemic target range may be more likely to benefit from multidomain interventions. Similar subgroup analyses based on glycemic

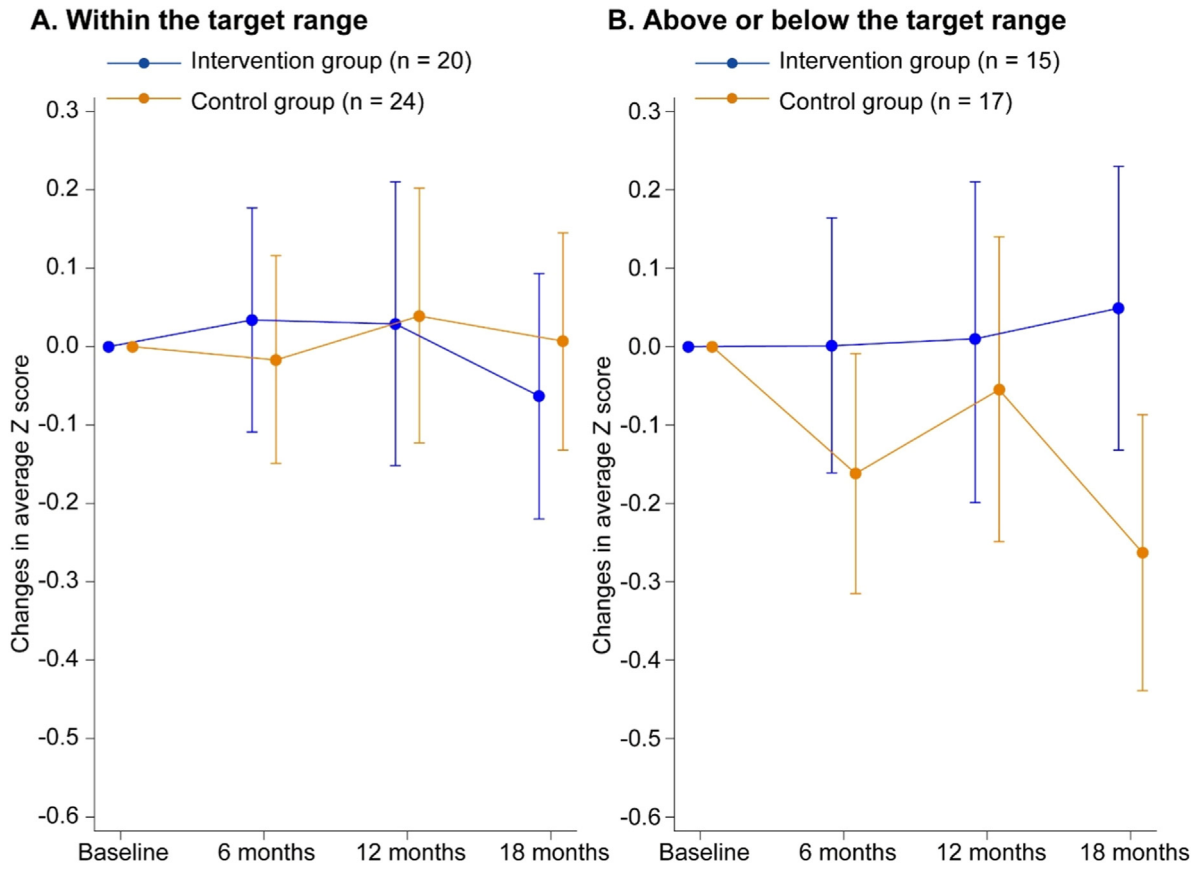

Figure 2. Changes in the average Z score from baseline to 18-month follow up according to glycemic control status at enrollment in participants with type 2 diabetes. The glycemic target range was HbA1c <7.0% without a lower limit for participants not receiving drugs potentially associated with severe hypoglycemia (insulin, sulfonylurea, or glinides) and 7.0%–7.9% for those receiving these drugs.

control status according to the JDS/JGS guidelines were conducted in the J-MIND-Diabetes [17]. Consequently, a cognitive improvement was detected in the intervention group among participants with HbA1c levels outside the target range; however, this trial did not demonstrate significant differences between the multidomain intervention and control groups [17]. Other recent studies have reported that HbA1c levels above and below the target range recommended by guidelines are associated with incident disability and mortality as well as incident dementia [21,35,36]. In the present study, individuals with HbA1c levels outside the target range in the control group experienced cognitive decline at the 18-month follow-up (change in Z score = −0.26, 95% CI = −0.44 to −0.09, Table 2). Therefore, this population may represent a priority target for interventions in diabetes management and dementia prevention. Further trials with larger sample sizes are required to confirm the effects of multidomain interventions on cognitive function and overall health outcomes.

The specific mechanisms by which multidomain interventions may benefit individuals with HbA1c levels outside the target range remain unclear. In this population, glycemic control status and medication use were not statistically different between the intervention and control groups at baseline and 18-month follow-up (Supplementary Table 8). Despite the absence of differences in metabolic control, there was a potential benefit on cognition, suggesting that factors beyond glycemic control contribute to cognitive outcomes. Previous observational and interventional studies have demonstrated an association of physical exercise [37], diet [7,38], and social and cognitive activities [8] with better cognitive function. However, a meta-analysis of five trials examining the impact of intensive glycemic control found no significant benefits for cognitive function [39]. These findings, along with the present study, suggest the relevance of a multidomain approach in promoting brain health in older adults with type 2 diabetes. Further analyses incorporating inflammatory markers, dementia-related blood biomarkers, and neuroimaging are warranted to elucidate the mechanisms underlying the multidomain intervention effects among this population.

No significant interaction was detected between intervention allocation and *APOE* status or the presence of memory impairment. Although several trials, including the J-MINT, have suggested that individuals with ≥1 *APOE* ε4 allele benefit more from multidomain interventions [16,40], we observed no such effect in our subgroup analyses. A possible explanation for this discrepancy is the lower proportion of individuals with ≥1 *APOE* ε4 alleles among participants with type 2 diabetes than that among participants without type 2 diabetes ($P = 0.047$). This finding suggests that the mechanisms underlying cognitive decline in individuals with diabetes differ from those in individuals without diabetes. An autopsy study indicated that diabetes is associated with vascular pathologies, such as lacunes, rather than Alzheimer's disease pathology [41]. Furthermore, the Look AHEAD study demonstrated beneficial effects of multidomain interventions on white mattery hyperintensities and cerebral blood flow, whereas there were no differences in total brain and hippocampal volumes [19,20], suggesting a potential role of vascular pathways in brain health in this population. Future analyses incorporating MRI-based outcomes, such as cerebral small vessel disease, may provide further insights into these mechanisms.

There were several limitations in this study. First, our results from this secondary subgroup analysis should be considered exploratory and interpreted as hypothesis-generating rather than conclusive. Second, the limited number of participants with type 2 diabetes and the wide CIs in the results suggest a low estimation accuracy. Third, there was no

detailed information on microvascular complications, which may have affected cognitive decline. Fourth, the intervention and follow-up durations in our study were shorter than those in other multidomain intervention trials [11,13,42]. Moreover, previous studies have reported that long-term pharmacologic interventions (≥3 years) can reduce the risk of dementia and cognitive decline [43–45]. Therefore, to clarify the preventive effects of multidomain interventions on dementia onset, longer intervention periods and follow-up trials are required. Another limitation of our study was the reliance on Z-score standardization across cognitive measures. While useful for statistical modeling, Z-transformation may obscure clinically meaningful effects, particularly in subgroups with distinct variance profiles or skewed baseline performances. This is especially relevant in aging populations, where ceiling or floor effects can distort the interpretation of standardized metrics. Therefore, we conducted an additional analysis using the MMSE as the outcome in the subgroups in which intervention effects were observed. At 18 months, the between-group difference was 1.25 points (95% CI = −0.60 to 3.10, p = 0.182) in the younger age group (65–74 years) and 2.50 points (95% CI = 0.67 to 4.33, p = 0.008) in participants with HbA1c levels outside the target range (Supplementary Table 9). Given that a decline of approximately 1.5 and 1.7 points on the MMSE is considered clinically important in cognitively unimpaired and MCI populations, respectively [46], these results may represent clinically significant differences. Finally, participants with type 2 diabetes had well-controlled glycemic status in this trial. More than half of the patients had HbA1c levels within the target range and none used insulin. Therefore, the generalizability of our findings to a broader population with diabetes may be limited. Additionally, the study cohort exclusively comprised older Japanese adults with relatively homogeneous ethnic and racial backgrounds. Broader contextual and environmental factors such as rurality, air pollution, social isolation, and access to healthcare were not evaluated. Thus, future studies conducted in more diverse populations that encompass a wider range of cultural, socioeconomic, and environmental contexts are warranted to improve the external validity of multidomain intervention strategies.

In conclusion, multidomain interventions did not demonstrate a significant efficacy in preventing cognitive decline among older adults with or without type 2 diabetes and MCI. Nevertheless, multidomain interventions may be particularly valuable for people with type 2 diabetes who are younger or whose glucose levels are not within the target range. Further analyses from other datasets with larger sample sizes or larger trials with prespecified hypotheses are required to confirm our findings.

Data availability

Anonymized data will be available upon request from any qualified investigator after clearance by the ethics committee.

Declaration of Generative AI and AI-assisted technologies in the writing process

No generative AI or AI-assisted technologies were used in the writing process of this manuscript.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Hidenori Arai reports financial support was provided by Japan Agency for Medical Research and Development. Taiki Sugimoto reports a relationship with Manpei Suzuki Diabetes Foundation that includes: funding grants. Taiki Sugimoto reports a relationship with Keiko-Yamasaki Memorial Funds that includes: funding grants. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Taiki Sugimoto: Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Paul K Crane:** Writing – review & editing, Methodology, Data curation. **Seo-Eun Choi:** Writing – review & editing, Validation, Methodology. **Kosuke Fujita:** Writing – review & editing, Conceptualization. **Jeanne Gallée:** Writing – review & editing, Methodology, Data curation. **Yujiro Kuroda:** Writing – review & editing, Conceptualization. **Michael Lee:** Writing – review & editing, Methodology, Data curation. **Nanae Matsumoto:** Writing – review & editing, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Akinori Nakamura:** Writing – review & editing, Methodology, Conceptualization. **Hisashi Noma:** Writing – review & editing, Validation, Supervision, Conceptualization. **Takuya Omura:** Writing – review & editing, Methodology, Conceptualization. **Ayaka Onoyama:** Writing – review & editing, Conceptualization. **Phoebe Scollard:** Writing – review & editing, Methodology, Data curation. **Kazuaki Uchida:** Writing – review & editing, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Yoko Yokoyama:** Writing – review & editing, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Hidenori Arai:** Writing – review & editing, Supervision, Project administration, Methodology, Funding acquisition, Conceptualization. **Takashi Sakurai:** Writing – review & editing, Supervision, Project administration, Methodology, Funding acquisition, Conceptualization.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jarlif.2025.100016.

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