Effects of Novel Cognitive Stimulating Activities (CSAs) on Cognitive Decline and Depressive Symptom: A Naturalistic Study

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Abstract

There is a scarcity of naturalistic follow-up studies on cognitive stimulating activities (CSAs), particularly in a real-world setting. We investigated a pooled novel CSA intervention to prevent cognitive decline amongst community-dwelling older adults without dementia. Within a cohort of older adults (N=991), four single-blinded randomized controlled trials involving four novel CSAs were conducted with a subset of the cohort (n=264). At cohort's 5-year follow-up, we examined if involvements in the CSAs improved cognition, compared to controls (n=727). The primary outcomes were changes in global cognition and cognitive domain scores measured by the mini-mental state examination (MMSE). Exploratory subgroup analyses stratified by baseline cognitive status and the number of CSAs were also conducted. Compared to the control group, there was a small improvement in the CSA group on the total MMSE score (d=0.108) and MMSE-immediate recall score (d=0.199). Furthermore, subgroup analyses revealed medium effect sizes of improvements (d=0.420) in cognitive domains in MCI (versus cognitively healthy) and those involved in two CSAs (versus one CSA). In summary, a CSA intervention improved cognition. MCI and those involved in two CSAs gained greater benefits from the CSAs. These sustained improvements in cognitive functions could have a significant impact on delaying or preventing dementia.

Introduction

With an aging population, dementia is one of the most urgent public health issues globally. However, despite intensified efforts and numerous attempts in pharmaceutical trials, no new pharmacological interventions have been discovered in the past decade [1], except one recent approval. Furthermore, the existing treatments for dementia have limited efficacy and are only effective for a short period (Birks, 2006). Hence, early prevention has become increasingly critical. Relatedly, validating the potentials of preventive non-pharmaceutical interventions (NPIs) to slow cognitive decline has received substantial attention in the past few years, particularly at the pre-clinical stage. Notably, if the onset and the progression of dementia could be delayed by just one year through any forms of interventions, there will be approximately 9.2 million fewer cases of dementia in 2050[2], equaling an 8% decrease in total projected dementia cases.

Numerous NPI trials to improve cognition have been conducted. These include the FINGER[3], PreDIVA[4], LipidiDiet[5], and MAPT[6] trials, with all but the FINGER trial showed overwhelmingly positive cognitive effects, owing to its intensive nature and high adherence rate[3]. These trials mainly focused on a myriad of traditional protective factors for dementia, specifically diet, the management of vascular risk factors, and physical activities. Cognitive stimulating activities (CSAs), a group of activities aimed at enhancing cognitive functioning[7], were not the central tenet. In 2006, The National Institute for Health and Care Excellence (NICE) guideline[8] recommended the regular use of CSAs for mild and moderate dementia. In 2017, a whitepaper commissioned by the Lancet also highlighted CSA as one of the preventive interventions with a high potential for delaying cognitive impairment[9,10]. Motivated by encouraging evidence gathered from multiple epidemiological studies, RCTs on CSAs to improve cognition have also

shown similar, albeit weaker evidence[11,12]. Furthermore, these RCTs were conducted over a short period (three months on average) with no follow-ups. A recent meta-analysis concluded evidence on the sustainability of CSA effects, with the effect sustained beyond CSA's facilitated sessions and up to a year[13]. Nonetheless, there has been scarce evidence on whether these effects can be sustained over an extended period well beyond one year. Despite many CSA interventions targeted at older adults with mild-to-moderate dementia[11,12,14], emerging evidence suggests that cognitively healthy older adults and individuals with mild cognitive impairment could also benefit from CSAs[15–18]. However, which diagnostic group could benefit the most from CSAs has been rarely investigated. Furthermore, whether the CSAs have a dose-response effect on multiple cognitive functions has not been adequately examined. Lastly, these previous trials on CSAs were often limited by small sample sizes (total N < 100) and particularly, uncertainty with regards to whether the effects are transferable to a real-world setting.

To address these gaps in knowledge, we studied a CSA intervention, utilizing a proof-of-concept naturalistic and pragmatic longitudinal follow-up study design. Within a longitudinal follow-up cohort, by pooling the four individual RCTs we have previously conducted nested within the cohort, we examined the pooled effects of involvements in four CSAs. The four CSAs were mindful awareness practice, horticultural therapy, arts and music reminiscence therapy, and choral singing. We previously found that these short-term CSAs improved multiple outcomes, specifically cognition, social connectedness[19–21], and biomarker measures [22,23]. In the current study, we sought to investigate over a five-year follow-up, if:

1) CSAs improve global cognition and cognitive functions across multiple domains;

2) CSAs improve depressive symptoms;
3) CSAs improve cognition and depressive symptoms differentially depending on the baseline cognitive statuses of study participants (MCI versus cognitively healthy) (exploratory sub-group analysis); and
4) There is a dose-response effect, with involvement in a higher number of CSAs eliciting greater improvements in outcomes (exploratory sub-group analysis).

Methods

Ethical Approvals & Study Registrations

The longitudinal follow-up cohort study was approved by the National University of Singapore Institutional Review Board (NUS-IRB) (Reference No: 10-517). All four trials involving the CSAs were also approved by the NUS-IRB (Reference No: B-14-110, B-15-016, NUS 2508, and B-16-095), and prospectively registered with the clinical trial database (Identifiers: NCT02286791, NCT02495194, NCT02919748, and NCT02854085, respectively). For all

studies, written informed consent was sought before study participation. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975.

Longitudinal Follow-up Cohort (N= 991)

The Diet and Healthy Aging (DaHA) is a multi-ethnic, community-based longitudinal follow-up cohort study, described extensively elsewhere [24]. The baseline recruitment period was from 2014 to 2017. For the follow-up, data collection was conducted from 2017 to 2020. Participants were followed up for a mean of 4.82 years (Figure 1).

CSA Intervention- Randomized Controlled Trials on CSAs (n=264)

From the larger DaHA cohort, participants were recruited for four separate RCTs, each involving a distinct CSA. The CSAs included mindful awareness practice (n=43), horticultural therapy (n=60), art and music reminiscence therapy (n=28), and choral singing (n=114). We conducted the four RCTs on four distinct CSAs from 2014 to 2019, a period between the DaHA baseline and follow-up. A total of 264 participants were involved in at least one of the four RCTs, and 19 participants of the 264 were involved in two RCTs (Figure 1). All RCTs on CSAs were single-blinded and two-armed, with the intervention periods ranged from six months to two years.

Due to word count limit, detailed descriptions of the inclusion and exclusion criteria for each RCT on the CSA can be found in the supplementary text. We pooled all the participants involved in at least one of the RCTs, which were assigned the group “CSA intervention” or the “CSA group”.

Non-Active Control Group (n=727)

Study participants in the longitudinal follow-up cohort study, who were not involved in any RCTs on CSAs, were denoted as controls.

Outcome variables Primary outcomes

Mini-Mental State Examination (MMSE) and MMSE Domains

MMSE is a brief 30-point cognitive screening questionnaire. It is one of the most commonly- used dementia screening tools, which enables the assessors to estimate the severity of cognitive impairment, as well as to track the course of cognitive changes over time. Each correct answer was awarded one point, with no points given for incorrect answers, or if the participant was unable to answer a question/perform an action. The score ranges from zero to 30, with a higher score indicating a higher cognitive performance. This study used a Mandarin-translated and modified version, which had been

adapted to local cultural contexts and norms and validated in the Singaporean population[25]. Apart from the total score indicating global cognitive function, the MMSE comprises sub-scales that assess multiple cognitive domains. They include MMSE-orientation (orientation), MMSE-immediate recall (immediate memory), MMSE-attention (attention span), MMSE-delayed recall (long-term memory), MMSE-language (language skills), and MMSE-construction (constructional and visual-spatial functions).

Secondary outcome

Geriatric Depression Scales (GDS)

GDS

The 15-item Geriatric Depression Scales (GDS) was used to assess depressive symptoms. The

participants rated 15 items with either Yes (1) or No (0) response categories[26]. The possible scores range from zero to 15, with a higher score indicating a higher depressive symptom. This scale has good psychometric properties in the Chinese population, with good internal consistency (Cronbach alpha of 0.83)[27].

Covariates

To control for possible confounding effects, established risk factors for cognitive decline which were collected as part of the main cohort were included as covariates in our analyses. They included the baseline scores for the respective outcome variables, baseline cases with probable depression and anxiety (presence/absence), age, sex, ethnicity (Chinese versus other ethnicities), the number of years of formal education, body-mass index (BMI), waist-to-hip ratio, the total number of self-reported chronic diseases, the total number of medication consumption (excluding psychotropic medications), and the total number of psychotropic medication consumption.

Statistical Analyses

To the best of our knowledge, this is a pilot and naturalistic study conducted with community-dwelling older adults, with a pooled CSA intervention nested. Hence, no *a priori* effect size was referenced. The differences in baseline variables were examined using Student's t-test, chi-square, or Fisher's exact tests, as the data necessitated. The raw scores for all the scales were transformed to Z-scores to enable cross-comparisons by directly comparing effect sizes. A linear mixed model was employed to examine the effects of the CSAs on the outcome measures, separately. All the participants included at baseline were

included in the analyses, as a linear-mixed model (LMM) accounts for lost-to-follow-up cases. In each model, the outcome of interest was entered as the dependent variable. Fixed effect terms included the time-points of the DaHA cohort (baseline and follow-up), treatment arm indicated by a dummy variable indicating either involved in the CSA intervention or control, and an interaction term between time-points and treatment arm. Baseline values of the respective outcome variables and the covariates described above were controlled for in all the models.

We noted that a participant can be enrolled in more than 1 RCT (and hence be involved in more than 1 CSA). We thus also noted their degree of involvement, which helped to address our exploratory aim on the postulated dose-response effects of the CSAs on outcomes. To address aims 3 and 4, we performed exploratory sub-group analyses, stratifying the total sample along the strata of 1) baseline cognitive statuses (MCI and cognitively healthy) and 2) the number of CSAs involved (2, 1 or 0), exploring their potential modifying effects on the outcomes. For all the analyses, all the participants involved in the intervention group were included in the analysis, based on the intention-to-treat principle. and the attendance rate was tested as a covariate.

All the analyses were performed using the Statistical Package for the Social Sciences (SPSS) Statistics for Windows, version 24.0 (IBM Corp., Armonk, N.Y., USA). For all the analyses, a two-tailed P-value of < 0.05 was considered statistically significant. Owing to the pilot nature of this study, we did not control for multiple testing[28], similar to previous studies of exploratory and hypothesis-generating nature[3,6]. Apart from interpreting P-values, statisticians have urged researchers to move away from solely interpretating findings based on p-values; Instead, effect size has been proposed to be a more informative index when interpreting findings[29], and thus was used as the primary index to assess intervention effects or lack thereof in this study. The effect size for each outcome in this study was indicated by Cohen's *d*. Since we analyzed Z-scores for all the outcome measures, Cohen's *d* was indicated by the estimate of the difference between the CSA and control groups, generated by the LMM[3,5]. Cohen's *d* of 0.2, 0.5, and 0.8 were considered small, medium, and large effect sizes, respectively[29].

Reporting of adverse events related to the intervention

Any adverse events were also closely monitored and reported.

Results

Baseline demographics

We excluded participants who received a diagnosis of dementia at baseline (n=19, 1.88% of the parent DaHA cohort), resulting in a final sample size of 991 participants. Due to the secondary analytic nature of this study, we had an approximately 1: 2.75 ratio of participants in the intervention group and the control

group, both for the total sample (n in CSA = 264, n in Control = 727) and for the MCI subgroup (n in CSA = 37, n in Control = 91). No significant differences were observed in all baseline variables between the CSA and control groups, except for sex and ethnicity (Table 1), i.e. a higher proportion of men and other ethnicities in the control group (P-values=0.008 and 0.034, respectively). Variables indicating baseline imbalance were controlled for in all the subsequent analyses. At 5-year follow-up, 612 participants were retained.

Table 1a

Comparisons of the baseline demographic and measures between participants in the Cognitively Stimulating Activities (CSA) and Control Groups (N= 991)

Baseline demographics and characteristics	CSA (n=264) Mean (SD) or n (%)	Control (n=727) Mean (SD) or n (%)	*p*-value
Cognitive Status			
Cognitively Healthy	227 (86)	636 (87.5)	0.592
MCI	37 (14)	91 (12.5)	
Age	74.95 (5.464)	74.85 (6.443)	0.817
Sex			
Men	58 (22)	222 (30.5)	**0.008****
Women	206 (78)	505 (69.5)	
Ethnicity			
Chinese	260 (98.5)	695 (95.6)	**0.034***
Other ethnicities (i.e. Malay & Indian)	4 (1.5)	32 (4.4)	
Years of formal education	6.48 (4.258)	6.25 (4.215)	0.434
BMI, kg/m^2	23.769 (3.717)	24.248 (4.153)	0.10
Waist-to-hip ratio	.872 (.088)	.876 (.089)	0.506
Total number of self-reported chronic diseases	2.494 (1.613)	2.530 (1.792)	0.778
Total number of medication consumptions (excluding psychotropic medications)	.023 (.149)	.017 (.196)	0.639
Total number of psychotropic medication consumptions	2.428 (2.301)	2.314 (2.345)	0.495
Probable Depression			
No	239 (90.5)	679 (93.4)	0.132
Yes	25 (9.5)	48 (6.6)	

Abbreviations: MCI=mild cognitive impairment; BMI= body mass index; Clinical cut-off for probable depression was GDS score≥ 5; bold values= p-values <0.10; * indicates *p*-value<0.05; ** indicates *p*-value<0.01.

Table 1b

Comparisons of the baseline scores for outcome measures between participants in the Cognitively Stimulating Activities (CSA) and Control Groups (N= 991)

Baseline demographics and characteristics	CSA (n=264) Mean (SD)	Control (n=727) Mean (SD)	*p*-value
Raw Scores			
MMSE Total Score	28.05 (2.110)	27.83 (2.352)	.175
MMSE - Orientation	9.74 (.532)	9.69 (.671)	.220
MMSE - Immediate Recall	2.96 (.191)	2.98 (.152)	**.082**
MMSE - Attention	4.23 (1.200)	4.08 (1.28)	.104
MMSE - Delayed Recall	2.50 (.0735)	2.43 (.744)	.202
MMSE - Language	7.73 (.553)	7.73 (.608)	.993
MMSE - Construction	.89 (.309)	.91 (.282)	.350
GDS	1.54 (1.876)	1.19 (1.985)	**0.015***
Z-Scores			
MMSE Total Score	.091 (.860)	-.000 (.959)	.175
MMSE - Orientation	.077 (.781)	.002 (.985)	.220
MMSE - Immediate Recall	-.043 (1.051)	.082 (.837)	**.082**
MMSE - Attention	.099 (.931)	-.016 (.997)	.104
MMSE - Delayed Recall	.080 (.980)	-.011 (.993)	.202
MMSE - Language	.017 (.890)	.012 (.979)	.993
MMSE - Construction	-.020 (1.039)	.045 (.948)	.350
GDS	0.126 (0.957)	-0.049 (1.012)	**0.015***

Abbreviations: MMSE, mini-mental state examination; GDS, geriatric depression scale; bold values= p-values <0.10; * indicates *p*-value<0.05; ** indicates *p*-value<0.01.

Effects of CSAs on total MMSE score, MMSE domain scores, and GDS scores

As shown in Supplementary Table 1 and Figure 2a & 3a, at follow-up, the CSA group had improved total MMSE score, while the controls had declined score (β = 0.108, 95% CI = -0.022 to 0.239, P =0.104); (Cohen's *d*=0.108). For the MMSE domain scores, there was

an increased MMSE-immediate recall score in the CSA group, compared to the controls (β = 0.199, 95% CI = 0.048 to 0.351, P = 0.010); (Cohen's *d*=0.199). Furthermore, there was a trend for CSAs to improve the MMSE-orientation score in the CSA group (β = 0.143, 95% CI = -0.017 to 0.303, P = 0.080); (Cohen's *d*=0.143). For all the other MMSE domain scores at follow-up, compared to the control group, all but MMSE-delayed recall scores had improvements in the CSA group, with small effect sizes ranging from 0.05 to 0.111.

For GDS score at 5-year follow-up, compared to controls, no difference was found between participants who have been involved in the CSAs, with a minimal effect size (Cohen's *d* = 0.012).

Sub-group Analyses - MCI

Supplementary Table 2a and Figure 2b & 3b show that in the MCI sub-group, there was a trend towards improvement in total MMSE score in the CSA group, compared to the control group (β =0.415, 95% CI= -0.051 to 0.880, P=0.081). Notably, in the CSA group, the total MMSE Z-scores improved from -0.33 to -0.097, while those in the control group deteriorated from -0.369 to -0.549, resulting in a medium effect size (Cohen's *d* = 0.415) (Figure 3b). Across all the MMSE domain scores, from baseline to follow-up, the domain scores in the CSA group improved. In contrast, those in the control group deteriorated. The effect sizes for the improvements ranged from small (0.199) to medium (0.413) (Figure 2b). For the GDS score, no difference was observed, with low effect size (β =0.051, 95% CI= -0.243 to 0.345, P=0.733) (Cohen's *d* = 0.030) (Supplementary Table 2a).

Sub-group Analyses - Cognitively Healthy

As shown in Supplementary Table 2b and Figure 2c & 3c, compared to the controls, the cognitive healthy sub-group had no increase in the total MMSE score, with very small effect size (Cohen's *d* = 0.072). For MMSE domain scores, compared to control, there was an increase in MMSE-immediate recall score in the CSA group (β=0.186, 95% CI= 0.040 to 0.332, P=0.013). The Cohen's *d* was 0.186, with the Z-scores in the CSA group improved from 0.020 to 0.072, while those in the control group deteriorated from 0.036 to -0.097. The other MMSE domain scores did not have improvements, coupled with small effect sizes. Furthermore, comparing the effect sizes with those of the MCI group, the effect sizes of improvements in the cognitively healthy sub-group were smaller across all the cognitive domains (Cohen's *d*, cognitively healthy: 0.027 to 0.186 versus MCI: 0.199 to 0.413). Similar to the MCI sub-group, there was no change in the GDS score, with Cohen's *d* = -0.001.

Sub-group Analyses - CSA Dose-Response

Supplementary Table 2c, Figure 2d, 2e & 3d showed that, for the total MMSE score, involvements in a higher number of CSAs were associated with a greater improvement in the total MMSE score. Those

involved in 2 CSAs had a larger effect size of improvement (Cohen's *d* = 0.183), compared to those involved in 1 CSA (Cohen's *d* = 0.102) (Figure 3d). Across the majority of the MMSE domain scores, the findings suggested higher effect sizes in those involved in 2 CSAs. Notably, the MMSE-orientation score trended towards greater increase in participants involving in 2 CSAs (β=0.418, 95% CI=-0.077 to 0.914, P=0.098), with a medium effect size (Cohen's *d* = 0.418) (Supplementary Table 2c). No changes in the GDS score at follow-up were observed, coupled with small effect sizes (1 CSA: Cohen's *d* = 0.019 VS 2 CSA: Cohen's *d* = -0.079) (Supplementary Table 2c).

Adverse events related to the intervention

No adverse event related to the interventions was reported.

Discussion

A pooled CSA intervention targeting community-dwelling older adults without dementia slowed cognitive decline and improved global cognition and multiple cognitive domains. Notably, improvements were noted in immediate memory, one of the earliest cognitive domains implicated in early cognitive decline. Exploratory subgroup analyses showed that the beneficial effects of the intervention were higher in MCI across *all* cognitive domains, with a medium effect size of 0.42 in global cognition and the visuospatial construction domain. Furthermore, involvement in a higher number of CSAs was associated with greater improvements in global cognition and several cognitive domains. On the other hand, involvement in the CSAs did not elicit improvements in depressive symptoms, regardless of baseline cognitive status and dose-response effect. In all, these findings suggest the high specificity and malleability of immediate memory in response to CSAs. Furthermore, greater effects of CSAs with MCI subgroup highlighted MCI as a potential interventional target population for CSAs.

A notable contribution of this study to the extant literature is the duration of follow-up and a control group. Till date, there are two existing main lines of evidence on the positive long-term effects of CSAs. First, several epidemiological studies have shown that participation in CSAs was associated with improved cognitive outcomes at approximately 5-year follow-up, but these studies were methodologically limited by the absence of control groups[30–32]. Second, in contrast to the overwhelmingly positive evidence from epidemiological studies on improving cognitive outcomes, RCTs on CSA interventions still present mostly mixed evidence[11,12,14,33]. They suffer from short follow-up periods and small sample sizes, raising concerns regarding the sustainability of the interventions. In the contrary, in our study conducted with pooled RCTs on CSAs in the cohort with mean follow-up of approximately five years, comparisons were made with a control group who had no prior involvements in any structured CSAs. We have thus addressed the limitations of short to intermediate-term follow-ups in prior studies, which also lacked control groups. Another noteworthy point is that not only did we show the positive effects of the CSAs on cognition, our effect size of 0.42 for global cognition in the MCI sub-group provide further evidence to the effect sizes summarized in a recent meta-analysis on RCTs on CSAs

and total MMSE score[13], extending the applicability to a real-world setting. Thus, for the first time, we showed pilot data on the long-term sustainability of CSAs' effects on improving cognitive functions over five years in a longitudinal and naturalistic setting. To the best of our knowledge, no other studies involving interventions comprising multiple CSAs, of similar large sample size, follow-up duration, study population, and study setting have been reported.

Next, we interpret our findings in the context of previous NPI RCTs on cognitive outcomes.
The FINGER trial showed overwhelmingly positive evidence of improvements in global and several domains of cognition following NPIs targeting traditional risk factors[3]. In contrast, the MAPT, preDIVA, LipiDiDiet, and ACTIVE trials[4–6,34], despite similarly incorporating NPIs and conducted over relatively long follow-up periods, did not result in cognitive improvements, and had small effect sizes. Compared to the FINGER trial's effect size of 0.12 for the combined neurocognitive test battery, the improvement of 0.102 in total MMSE in our total sample is strikingly similar. Notably, we extended the literature by showing pilot data on an effect size of 0.42 for the improvement in global cognition in the MCI sub-group upon undergoing CSA intervention. Furthermore, it is noteworthy that the relatively larger effect sizes detected in this study should be considered in the context of a less intensive nature of our CSA intervention. This is in stark contrast with previous studies, which involved intensive interventions modalities, such as regular exercises and multiple follow-ups with physicians (4). Our CSA intervention also improved immediate memory, a cognitive domain tapping on lower cognitive load, with an effect size of approximately 0.2 in the total sample and both the healthy aging and MCI subgroups. This phenomenon might be attributed to the distinct advantages of CSAs, in that interventions with solely CSAs could be more efficacious, compared to a mix of intervention modalities targeting the traditional risk factors of dementia[4–6,34].
Concurring with previous studies, compared to controls, cognitive functions tapping on higher cognitive load, such as executive functions, were not improved in our study. We did not follow up with the participants on whether they continued pursuing the CSAs at the end of participation in the RCTs. With this caveat, by showing improved cognition after five years, we showed the sustained beneficial effects conferred by the CSAs, independent of continued pursuance of CSAs upon conclusion of the facilitated sessions.

A primary novelty of this study was the subject recruitment from the community rather than clinical settings and the continuous follow-up in the same setting, providing a real-world context. This communal setting also allowed us to examine the naturalistic effect of CSAs with both cognitively healthy and mildly impaired community-dwelling older adult populations in a single study. Compared to cognitively healthy participants, those with MCI had higher gains in global cognition and *all* cognitive domains. This finding lends empirical evidence to the hypothesis postulating that MCI is a pre-clinical stage at which the older adults can still learn new skills[35], and likely reap higher benefit than cognitive healthy. Similarly, a behavioural trial conducted with African-Americans also showed delayed cognitive decline in individuals with MCI upon undergoing intervention[36]. Concurring with evidence from prior studies[6,37], we postulate that the CSAs were most effective with MCI. For cognitive healthy older adults, there could either be a ceiling effect on MMSE, or they require more extended, more intensive and/or interventions

other than CSAs to achieve similar effect sizes of cognitive improvement as MCI. Additionally, with higher involvement in the CSAs, there were also higher effect sizes of improvements in global cognition and several cognitive domains. Hence, these showed pilot findings suggesting that the potential greater benefits of participation in a higher number of CSAs in a naturalistic and real-world setting. Coupled with no adverse event related to either the MAP or HEP intervention was reported, the CSA intervention was both safe and feasible.

Limitations & Future Directions

This study has several limitations. The main limitation was the potentially underpowered sample size, which might have rendered statistical insignificance, even with improvements with medium effect sizes, i.e. 0.42, detected in three cognitive outcomes. However, interpreting results solely based on p-values have been de-emphasized, as it informs us statistical significance without providing any useful information on the clinical effects of treatments, and studies have started to report the clinical effects based on effect sizes to inform clinical significance. In our study, we have presented both statistics for readers' interpretations, and highlighted the medium effect sized improvements in multiple cognitive domains. There was also some degree of heterogeneity in the pooled RCTs. However, the heterogeneity reflects the characteristics of a real-world and naturalistic study[6]. We also could not exclude the possibility that the participants could have been involved in other unstructured CSAs outside the structured CSAs performed in the study. Since this information was unavailable, it leaves the plausibility of residual confounding. As this issue is an inherent limitation of a naturalistic, pragmatic and real-world study such as ours, it could be mitigated in future studies, such as employing an RCT design for the total study sample. Similarly, potential confounders, such as physical activity and social networks were not assessed in the main cohort and thus were not controlled for in this study. We did not have data for the attendance and adherence rates as covariates, and it was not in our study protocols to follow-up with the participants on whether they continued pursuing the CSAs after the conclusions of the RCTs. Thus, future studies should collect data on and examine continual pursuance and intervention adherence. It is worth noting that had most of the participants in our study continued the CSAs beyond the facilitated sessions, the effect sizes for cognitive improvements could have been even larger than currently observed, further supportive of our findings. Lastly, our sample population was recruited from a single study site, and thus may not be representative of the whole population, warranting future validations in larger and more representative study population.

Strengths of the study

This study represents a significant advancement in the literature on CSA intervention and cognition and depressive symptoms in several aspects. First, all previous studies on CSAs and cognition either employed an epidemiological design with up to five-year follow-up without control groups, or a short-term RCT design without long-term follow-up. Even with an RCT, most studies on CSA did not have long-term

follow-up period beyond one year. The previous RCTs were also limited by having small sample sizes (N<100). In contrary, our study contributed to the literature by having conducted the largest and the longest RCTs examining different CSAs on cognition nested within a longitudinal cohort, further incorporating depressive symptom as the secondary outcome. Second, with our *a priori* inclusions of two distinct neuropsychiatric outcomes, cognition and depressive symptoms, we holistically examined CSAs' multi-faceted effects, revealing differential effects of the intervention on the measures. Third, the cognitive status of the participants was diagnosed during our team's monthly consensus panel meetings, using the well-established clinical diagnostic guidelines, lending robustness to our study and derived findings. Conversely, many previous studies utilized MMSE cut-off scores to derive cognitive status, likely introducing inaccuracies in diagnoses[25,38]. Recruitment on community-dwelling older adults at the pre-clinical dementia stage allowed us to stratify our sample into clinically defined cognitively healthy and MCI sub-groups, showing the superiority of CSAs with MCI over cognitively healthy older adults.
Fourth, with multiple CSA interventions, study participants could be involved in more than one CSA, allowing us to examine dose-response effects. Fifth, being conducted in an RCT setting, the CSAs were formally and structurally conducted, with fixed intervention durations, pre-planned programs for each session, and with frequencies of the interventions objectively quantified. This study design mitigates a core limitation present in previous epidemiological studies with CSAs, in which the study participants self-reported information on CSA participation. These previous subjective reports could have introduced recall bias[39] and thus compromised previous findings. Lastly, apart from being conducted as a pilot study, a distinctive feature of our
study is the unique model and setting in which we employed to recruit participants. Many previous non-pharmacological intervention RCTs on cognition were either recruited from or based entirely in clinical settings. With our research centre located inside a shopping mall, we recruited solely community-dwelling older adults. Hence, this unique setting allowed us to conduct interventions solely *in* the community and *for* the community, enhancing the generalizability and external validity of our findings[4]. Embedded within this pragmatic and naturalistic setting, the Hawthorne effect[4,40] could have been minimized with our real-world data.

Conclusions And Implications

With a community-based design, our study provided a novel and pragmatic model for future research examining a CSA intervention in a real-world setting, intervening and preventing cognitive decline at the pre-clinical stage. With this community-based model, our findings could significantly impact on public health. Notably, we adopted primarily a public health approach, targeting a multi-ethnic cohort of community-dwelling older adults. Cognitive decline or even a lack of improvement in response to interventions, such as those in our control group, could signal future cognitive impairment and pathology[41], of which our previous studies with these CSAs concur[22,23]. In the natural course of ageing over five years, cognition inevitably decline. Notably, with up to medium effect sizes of improvements associated with the CSA intervention, given an even more extended follow-up period, these cognitive improvements could potentially translate into quantifiable clinical impacts, such as decreased incidence

of dementia. Lastly, the CSA intervention has several unique features, including a partnership with a non-governmental organization in a community setting, and by design, easy-to-implement, low-cost, and most importantly, pragmatic yet effective and without any adverse events reported. Thus, it could be easily replicated and implemented in other countries and a wide range of other settings. Ultimately, this novel model could potentially improve global public health, delaying or preventing the development of dementia.

Declarations

Data Availability

Data available upon request at the discretion of the authors.

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Author Contributions

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Competing interests

The author(s) declare no competing interests.

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Figures

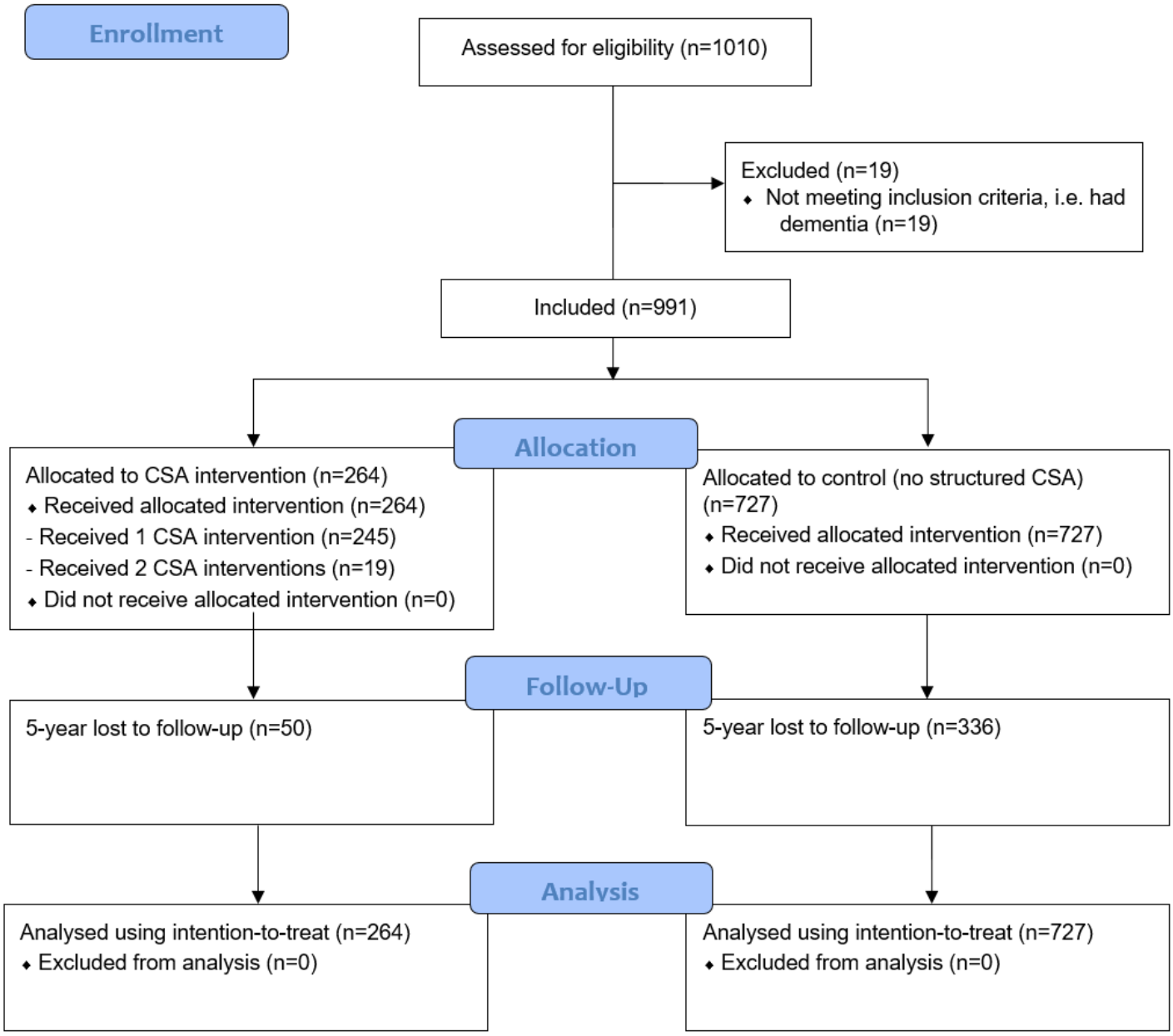

Figure 1

CONSORT 2010 Flow Diagram

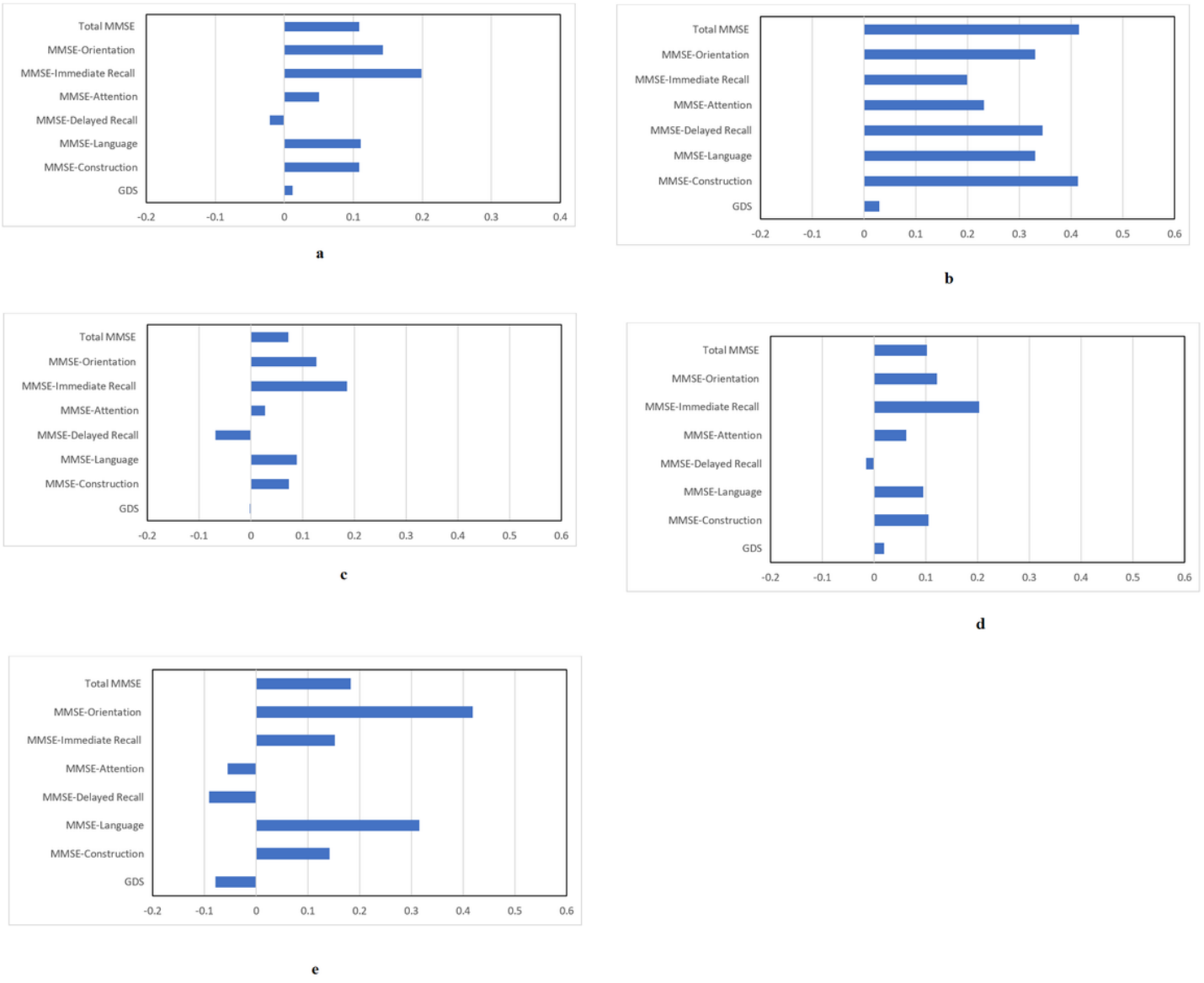

Figure 2

a. Effect Sizes (Cohen's d) of Cognitive Stimulating Activities (CSAs) on Outcome Measures - Total Sample Footnote: MMSE, mini-mental state examination; GDS, geriatric depression scale; For interpreting Cohen's d values, since the reference group was the control group, positive value indicates increase in CSA and vice-versa. Positive Cohen's d values for MMSE and its domain scores indicate improvements in cognitive function, whereas negative Cohen's d value for GDS indicate improvements in depressive symptoms. b. Effect Sizes (Cohen's d) of Cognitive Stimulating Activities (CSAs) on Outcome Measures - MCI Sub-group Footnote: MMSE, mini-mental state examination; GDS, geriatric depression scale; For interpreting Cohen's d values, since the reference group was the control group, positive value indicates increase in CSA and vice-versa. Positive Cohen's d values for MMSE and its domain scores indicate improvements in cognitive function, whereas negative Cohen's d value for GDS indicate improvements in depressive symptoms. c. Effect Sizes (Cohen's d) of Cognitive Stimulating Activities (CSAs) on Outcome Measures - Cognitively Healthy Sub-group Footnote: MMSE, mini-mental state examination; GDS, geriatric

depression scale; For interpreting Cohen's d values, since the reference group was the control group, positive value indicates increase in CSA and vice-versa. Positive Cohen's d values for MMSE and its domain scores indicate improvements in cognitive function, whereas negative Cohen's d value for GDS indicate improvements in depressive symptoms. * the effect size of GDS was very close to 0, hence hardly visible on the figure. d. Effect Sizes (Cohen's d) of Cognitive Stimulating Activities (CSAs) on Outcome Measures - Involvement in 1 CSA Footnote: MMSE, mini-mental state examination; GDS, geriatric depression scale; For interpreting Cohen's d values, since the reference group was the control group, positive value indicates increase in CSA and vice-versa. Positive Cohen's d values for MMSE and its domain scores indicate improvements in cognitive function, whereas negative Cohen's d value for GDS indicate improvements in depressive symptoms. e. Effect Sizes (Cohen's d) of Cognitive Stimulating Activities (CSAs) on Outcome Measures - Involvement in 2 CSAs Footnote: MMSE, mini-mental state examination; GDS, geriatric depression scale; For interpreting Cohen's d values, since the reference group was the control group, positive value indicates increase in CSA and vice-versa. Positive Cohen's d values for MMSE and its domain scores indicate improvements in cognitive function, whereas negative Cohen's d value for GDS indicate improvements in depressive symptoms.

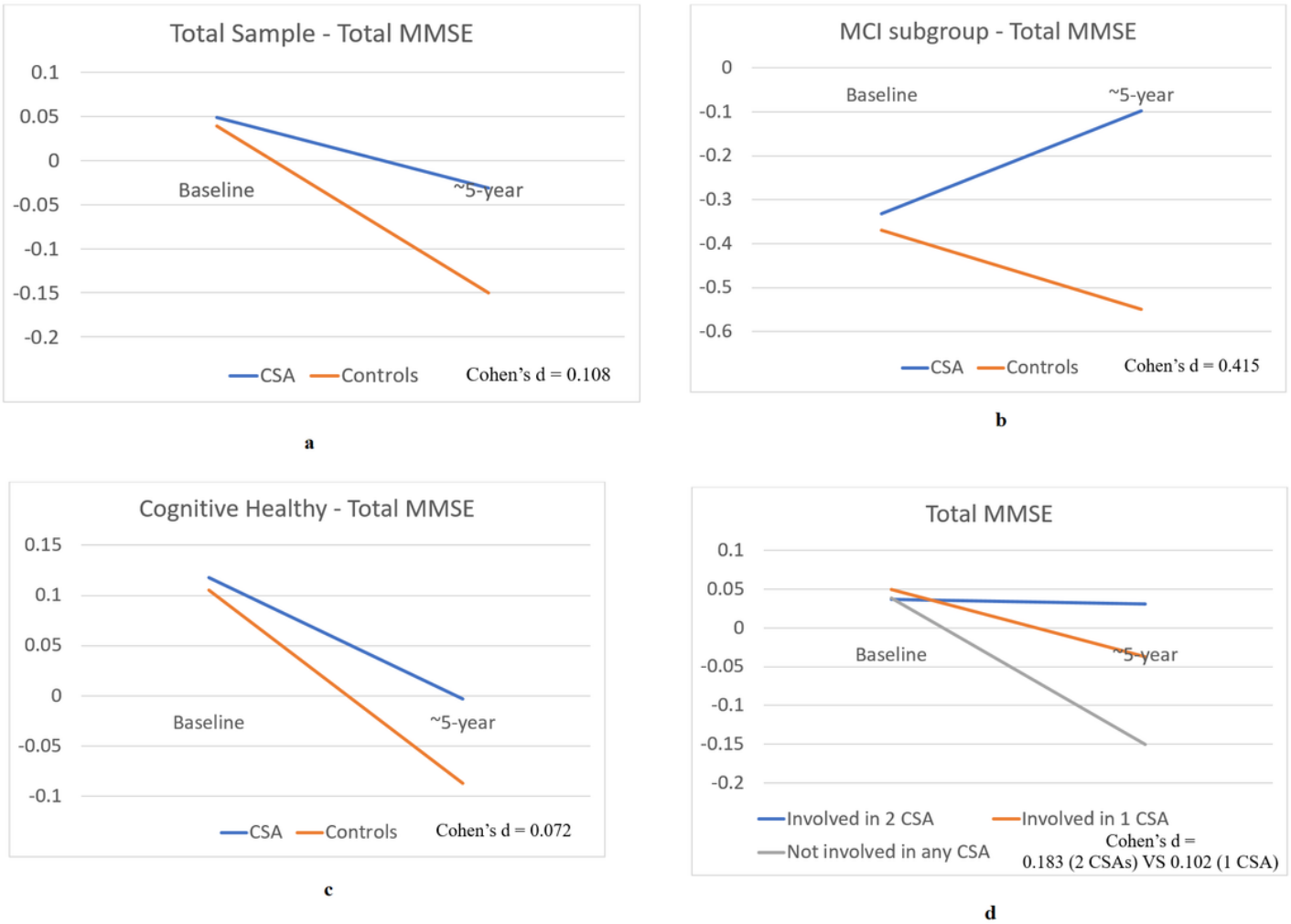

Figure 3

a. Effect and Effect Size (Cohen’s d) of Cognitive Stimulating Activities (CSAs) on Mean Global Cognition - Total Sample b. Effect and Effect Size (Cohen’s d) of Cognitive Stimulating Activities (CSAs) on Mean Global Cognition – MCI subgroup c. Effect and Effect Size (Cohen’s d) of Cognitive Stimulating Activities (CSAs) on Mean Global Cognition – Cognitive healthy subgroup d. Effect and Effect Size (Cohen’s d) of Cognitive Stimulating Activities (CSAs) on Mean Global Cognition – Dose-response effect

Supplementary Files

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