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TITLE PAGE

TITLE: Moderators of cognitive outcomes from an exercise programme in people with mild to moderate dementia

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Running Header: Moderators of cognitive outcomes to exercise

IMPACT Statement: We certify that this work is novel of recent novel clinical research.

The potential impact of this research on clinical care or health policy includes the following: (1) consideration on whether exercise should be offered to people with mild to moderate dementia; (2) suggestion that not all people with mild to moderate dementia have comparable clinical outcomes to exercise interventions; and (3) provides evidence for stratification of exercise prescription for people with mild to moderate dementia.

ABSTRACT

OBJECTIVES: To estimate whether baseline participant variables were able to moderate the effect of an exercise intervention on cognition in patients with mild to moderate dementia.

DESIGN: Subgroup analysis of a multi-centre, pragmatic, randomised controlled trial.

SETTING: Community-based gym/rehabilitation centres

PARTICIPANTS: 494 community-dwelling participants with mild to moderate dementia.

INTERVENTION: Participants were randomised to a moderate- to high-intensity aerobic and strength exercise programme or a usual care control group. Experimental group participants attended twice-weekly gym sessions for 60 to 90 minutes duration for four months. Participants were prescribed home exercises for one additional hour per week during the supervised period, and 150 minutes each week after the supervised period.

MEASUREMENTS: Multi-level regression model analyses were undertaken to identify individual moderators of cognitive function measured through the ADAS-Cog at 12 months.

RESULTS: When tested for a formal interaction effect, only cognitive function assessed by the baseline number cancellation test, demonstrated a statistically significant interaction effect (-2.7 points; 95% confidence interval: -5.14 to -0.21).

CONCLUSIONS: People with worse number cancellation test scores may experience greater progression of cognitive decline in response to a moderate- to high-intensity exercise programme. Further analyses to examine whether these findings can be replicated in planned, sufficiently-powered analyses are indicated.

Keywords: cognitive function; dementia; physical activity; prediction; DAPA

INTRODUCTION

Dementia is a global health and social care challenge. Approximately 50 million people worldwide have dementia.[1] No effective interventions are available which cure or directly modify the course of dementia.[2] The hypothesis that aerobic and strengthening exercise may slow cognitive impairment in dementia has gained widespread popularity. Studies describe plausible mechanisms using mammalian models.[3] Recent systematic reviews of trials of exercise training in people with dementia present conflicting findings.[4,5] These confirm the multiplicity of small studies of low methodological quality, limited duration of follow-up and high unexplained heterogeneity in findings.

We recently reported a randomised controlled trial investigating the effect of a moderate- to high-intensity aerobic and strength exercise training programme on cognitive impairment at 12 months in 494 community-dwelling people with mild to moderate dementia.[6] This targeted known mechanistic pathways in vascular and Alzheimer's type dementia. At 12-month follow-up, the mean Alzheimer Disease Assessment Scale Cognitive (ADAS-Cog) score increased to 25·2 (standard deviation (SD): 12·3) in the exercise group and 23·8 (SD: 10·4) in the usual care group (indicating worse cognitive impairment in the exercise group).[6] *A priori* subgroup analyses found no evidence for gender, standardised mini-mental state examination (sMMSE) score, prior mobility or type of dementia modifying cognitive function.[6] However, other theoretically plausible subgroups were not tested. Given these results suggest that the intervention could adversely affect cognitive function, this analysis aimed to estimate whether baseline participant variables were able to moderate the effect of the exercise intervention on cognition in patients with mild to moderate dementia.

METHODS

The design, intervention and main analysis results for the DAPA trial have been reported elsewhere.[6,7]

Participants and randomisation

In brief, 494 community-dwelling people with mild to moderate dementia were recruited from 15 regions across England. People were eligible if they had a clinically-confirmed diagnosis of dementia

according to the Diagnostic and Statistical Manual 4th Edition (DSM-IV)[8] and a sMMSE of greater than 10.[9] Participants were randomised 2:1 in favour of an experimental exercise arm.

Interventions

The experimental intervention was a moderate- to high-intensity aerobic and strength exercise programme. Participants attended twice-weekly gym sessions for 60-90 minutes in duration for four months. Participants were prescribed home exercises for one additional hour per week during the supervised period, and thereafter, prescribed a more frequent home-based programme with a target of 150 minutes per week unsupervised physical activity or exercise. Behavioural strategies were used to promote adherence during the supervised programme.[10] Telephone-administered motivational interviews were used to promote adherence after the supervised programme.

Participants in the control group received usual care. This included counselling for carers and families, a clinical assessment, prescription of symptomatic treatments and brief advice about physical activity.

Outcome Measure

Data were collected at baseline, six and 12-months. The outcome of interest in the main trial was the ADAS-Cog at 12 months.[11] This is an 11-item, participant-rated scale, scored 0-70; higher scores indicate worse cognitive impairment. It includes praxis, memory, language, number cancellation and maze test subscales. Trained interviewers administered the cognitive function measures in participant's homes. A four-point change is regarded a clinically important within-person change at six months,[12] and a seven-point change at 18 months.[13] A between-group difference of two to three points is regarded as a worthwhile target for clinical trials.[14] For the purposes of these sub-group analyses, the primary outcome was change from baseline to 12 months.

Statistical Analyses

We undertook sub-group analyses to identify groups of participants who may have responded better or worse to the exercise intervention. To maintain acceptable statistical power, we selected only pre-randomisation variables where there were data for a minimum of 50% of participants in the exercise intervention cohort (i.e. 164).[15] Baseline variables which met this criteria were: age; participant living arrangement (alone/with others); number of medications prescribed; baseline ADAS praxis, memory and language subscales and the number cancellation test; EQ-5D-3L health-related quality of

life (HRQOL) (higher scores indicate worse health state; participant-rated);[16] Quality of Life Alzheimer's Disease (QoL-AD) scale (scored 13-52, higher scores indicating better perceived quality of life; participant-rated);[17] the Neuropsychiatric Index (NPI) (scored 0-144, higher scores indicating increased behavioural and psychological symptoms; carer-rated);[18] and the Bristol Activities of Daily Living (BADL) Index (scored 0-60, higher scores indicating greater impairment; carer-rated).[19]

We used bar charts to visualise the dispersal of change in ADAS-Cog from baseline to 12-month follow-up across both groups. We estimated treatment effects using change from baseline (baseline minus follow-up). To ensure that baseline differences did not influence analyses, we adjusted the models for the baseline variable. As there is no published guidance on relevant cut-points for the variables of interest, we used a median cut-point.[20]

To assess for sub-group effects, we fitted multi-level regression models with an interaction term (treatment by subgroup interaction) while adjusting for age, gender, baseline of the dependent variable and baseline sMMSE. Region was included as a random-effect. We also undertook complier average causal effect (CACE) analyses to determine whether there was any treatment effect modification on the primary outcome for those who complied with treatment. Compliance was defined *a priori* as attending 22 out of a maximum 30 group sessions (75%). The sub-group effect estimate, 95% confidence interval (CI) and P-value were reported for each analysis.

Data were imputed using recognized item-level multiple imputation techniques for the primary outcome (ADAS-Cog).[21] No missing data was imputed for any other variable.

All statistical tests were two-sided. Statistical significance was assessed at the five percent level. All analyses were conducted using Stata version 15.1 (StataCorp, Texas, USA).

RESULTS

Cohort Characteristics

From 494 participants randomised, data were available for the primary outcome at 12 months for 137/165 (83%) of usual care and 281/329 (85%) of exercise group. Baseline demographic and clinical characteristics for the trial cohort are presented in **Table 1**. These are presented for each subgroup by variable in **Table 2**.

Dispersal of ADAS-Cog Results

Figure 1 illustrates the change in total ADAS-Cog score from baseline to 12 months for each group. There was a positive change (improved cognitive function) in 49/137 participants (36%) of the usual care group, and 80/281 participants (29%) of the exercise group. There was a negative change (cognitive decline) in 86/137 participants (63%) of the usual care group, and 198/281 participants (71%) of the exercise intervention group.

Principal Analysis

When tested for a formal interaction effect, only cognitive function assessed by the baseline number cancellation test demonstrated a statistically significant interaction effect (-2.7 points; 95% CI: -5.14 to -0.21; P=0.03). This remained present as the only variable with an interaction effect in the CACE analysis (-3.7 points; 95% CI: -7.23 to -0.21; P=0.04) (**Table 2**). There was no evidence of treatment modification for all other variables (**Table 2**).

Inspection of within-strata changes suggest that cognitive decline was greater for eight variables (**Table 2**). Cognitive decline was greater in those aged over 78 years (-1.7 points; 95% CI: -3.41 to -0.04), those with greater dementia-related behaviours (NPI greater 8 points) at baseline (-2.6 points; 95% CI: -4.64 to -0.53) and reduced activities of daily living with a BADLs score of greater than 11 points (-2.2 points; 95% CI: -4.27 to -0.06). Cognitive decline was greater for those who lived with others (-1.6 points; 95% CI: -2.96 to -0.24). People with worse cognitive function at baseline in terms of overall function (ADAS-Cog total score greater than 20 points) and all sub-scales (language (greater 2 points), memory (greater 17 points), praxis (greater than 1 point) and number cancellation (greater than 3 points) demonstrated greater cognitive decline (**Table 2**).

DISCUSSION

This exploratory analysis has identified that participants with worse number cancellation test scores at randomisation, may experience greater progression of cognitive decline in response to a moderate-to high-intensity exercise programme. No other variable moderated participant response to treatment. Though the within-strata effects illustrate that those who underwent the exercise intervention demonstrated greater cognitive decline, these changes were small. Due to the nature of exploratory analyses, these findings should be viewed with caution before replicating with sufficiently powered cohorts.

Whilst previous systematic reviews have concluded that exercise may have limited impact on altering cognitive performance for people with cognitive impairment *per se*,[22,23] this subgroup analysis indicated that this may not be the case for everyone. The finding that people with poorer number cancellation test score may experience greater progression of cognitive decline offers a signals that exercise may 'harm' some individuals. However, physical activity is advocated for older people with and without cognitive impairment, for a variety of health effects.[6,24] It is therefore imperative that the results of this subgroup analysis are rigorously explored before consideration is made to change physical activity recommendations for people with mild to moderate dementia.

Only pre-randomisation number cancellation test demonstrated an interaction effect with cognitive outcome. No other measures of cognitive impairment demonstrated such an interaction effect after exercise. This emphasises that the ADAS-Cog measures impairment in multiple cognitive domains across the subscales.[25] There is no clear reason why only a number cancellation test would predict greater cognitive decline following an exercise programme. It may be that number cancellation test demands a higher attentional load, particular in relation to selective attention in visuo-spatial memory, compared to the other tests.[26] However Halloway et al's[27] previous assessment of the interaction between physical activity and cognitive activity, based on 742 older adults in the USA, suggests that any interaction may be attributed to memory rather than perceptual speed or visuospatial ability. Given this uncertainty, further research to understand why number cancellation test score should differ to other domains of cognitive function is warranted.

The results of the CACE analysis indicate that compliance to the exercise programme was not associated with cognitive outcomes. It was not the purpose of this trial to assess the association between exercise dose-response and outcome. Previous literature has focused on the relationship between exercise intensity and outcome. This suggests that moderate- to high-intensity exercise is more effective at improving cognitive outcomes compared to lower-intensity exercise.[28] This is based on the principle that moderate- to high-intensity exercise drives synthesis and accumulation of neuroactive metabolites including myokines and ketone bodies, to enhance brain-derived neurotrophic factor expression.[29] However, it remains unclear whether there is a threshold related to frequency of exercise and outcome for people with mild or moderate cognitive impairment.[30]

This analysis presented with three key limitations. Firstly, this analysis was not powered for these exploratory subgroup analyses. Brookes et al[15] recommend that sample sizes should be up to four times larger to power an interaction test within a subgroup analysis. Furthermore the unequal group allocation adopted in this trial compounded the issue of power for these analyses. Therefore, as with any subgroup analysis, the results should be interpreted with caution and the findings considered as

hypotheses. Secondly, data on exercise compliance and fidelity of the intervention was based on treatment logs and self-reported diaries. Whilst previously reported as a useful indicator,[31] it remains unclear to what extent exercise adherence and specifically the degree of exertion undertaken within exercise regimes, was met. Finally, the NPI could only be completed if the carer was a resident carer i.e. lived with the participant or if the carer was a non-resident but provided 16 or more hours of care per week, and had knowledge of night-time behaviours. Accordingly there was fewer data for this outcome, which reduced the power of this outcome's analysis.

CONCLUSION

This exploratory analysis indicates that people with poorer number cancellation scores at baseline had greater cognitive decline after a moderate- to high-intensity exercise programme. The differences were small over the time period assessed. Further analyses are indicated to examine whether these findings can be replicated in planned and sufficiently-powered analyses.

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Author Contributions:

1) Substantial contributions to conception and design: TS, DM, HL, SD, SF, BF, VPN, BS, SEL
2) Acquisition of data: DM, HL, SEL
3) Analysis and interpretation of data: TS, DM, HL, BF, BS, SEL
4) Drafting the article: TS, DM, HL, BF, SEL
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FIGURE AND TABLE LEGENDS

Table 1: Baseline demographic and clinical characteristics of all randomised participants.

Table 2: Subgroup analyses where cognition is the outcome of interest at 12 months. Values are number of participants, mean (standard deviation) unless stated otherwise.

Figure 1: Bar chart to illustrate the percentage of cohort who demonstrated change in ADAS-Cog score from baseline to 12 months for usual care and exercise group participants.

Table 1: Baseline demographic and clinical characteristics of all randomised participants.

Characteristic	Usual care (N=165)	Exercise (N=329)
Age (years), mean(SD)	78·4 (7·6)	76·9 (7·9)
Gender (male), n (%)	106 (64·2%)	195 (59·3%)
Living arrangements, n (%)		
Live alone	35 (21·2%)	62 (18·8%)
Live with relatives/partner/friends	130 (78·8%)	267 (81·2%)
Total number of medications taken, mean(SD)	5·5 (3·1)	5·7 (3·7)
ADAS-Cog, mean(SD)	21·8 (7·7)	21·4 (9.6)
Language subscale, median (IQR)	2 (1 to 4)	2 (0 to 4)
Memory subscale, mean(SD)	17·4 (4·8)	16·7 (6·2)
Praxis subscale, median (IQR)	1 (1 to 2)	1 (1 to 2)
sMMSE, mean(SD)	21·6 (4·6)	22·0 (4·7)
sMMSE catagorised, n (%)		
No cognitive impairment (24-30)	70 (42.4%)	142 (43.2%)
Mild cognitive impairment (19-23)	53 (32.1%)	110 (33.4%)
Moderate cognitive impairment (10-18)	42 (25.5%)	77 (23.4%)
EQ-5D-3L (self-reported), mean(SD)	0·85 (0·18)	0·82 (0·20)
QoL-AD (self-reported), mean(SD)	39·3 (5·2)	38·7 (5·6)
NPI (proxy-reported), median (IQR)	10 (3 to 20)	7.5 (3 to 17.5)
BADL (proxy-report), median (IQR)	10 (5 to 16)	11 (6 to 17)
ZBI, mean(SD)	29·0 (15.7)	30·6 (15·4)
Carer EQ-5D-3L, mean(SD)	0·82 (0·23)	0·79 (0·21)

ADAS-Cog - Alzheimer Disease Assessment Scale cognitive sub-scale; BADL – Bristol Activities of Daily Living index; IQR – inter-quartile range; NPI – neuropsychological index; QOL-AD - Quality of Life Alzheimer's Disease; sd – standard deviation; sMMSE - standardised mini-mental state examination score; ZBI - Zarit Burden Interview

Table 2: Subgroup analyses where the change in cognition from baseline to 12 months is the outcome of interest.

Variable	Subgroup	Usual Care		Exercise programme		Within stratums: effect estimate (95% CI)	Interaction effect (95% CI); P-value	CACE analysis* Interaction effect (95% CI); P-value
		Baseline	12 months	Baseline	12 months			
Age (years)	≤78	67; 21.9 (8.8)	59; 25.2 (12.3)	173; 21.5 (10.2)	147; 25.9 (13.7)	-0.8 (-2.67, 0.95)	-0.9 (-3.35, 1.62); 0.49	-1.1 (-4.59, 2.43); 0.55
	>78	96; 21.7 (6.8)	78; 22.8 (8.6)	156; 21.4 (8.9)	131; 24.5 (10.6)	-1.7 (-3.41, -0.04)		
Living arrangements	Live alone	34; 19.4 (7.3)	29; 21.0 (9.1)	62; 19.3 (8.0)	46; 20.9 (9.8)	-0.3 (-3.10, 2.48)	-1.3 (-4.39, 1.81); 0.42	-1.8 (-6.80, 3.20); 0.48
	Live with others	129; 22.4 (7.7)	108; 24.6 (10.6)	267; 21.9 (9.9)	232; 26.1 (12.6)	-1.6 (-2.96, -0.24)		
Total number of medications	≤4	62; 20.4 (6.4)	51; 22.0 (8.1)	142; 22.7 (9.9)	124; 26.5 (12.9)	-1.4 (-3.41, 0.52)	0.2 (-2.34, 2.83); 0.85	0.2 (-3.50, 3.75); 0.95
	>4	92; 22.5 (8.6)	78; 25.0 (11.9)	176; 20.2 (9.1)	146; 24.1 (11.8)	-1.2 (-2.86, 0.46)		
ADAS-Cog	≤20	74; 15.5 (3.1)	67; 18.2 (6.6)	170; 14.0 (3.6)	144; 16.8 (6.3)	-0.3 (-2.05, 1.39)	-2.1 (-4.53, 0.38); 0.10	-2.5 (-5.99, 1.09); 0.17
	>20	89; 27.0 (6.4)	68; 29.4 (10.6)	159; 29.4 (7.4)	134; 34.3 (10.7)	-2.4 (-4.16, -0.66)		
Language subscale	≤2	96; 17.5 (4.3)	83; 19.3 (6.9)	201; 16.4 (5.9)	173; 19.5 (8.3)	-1.0 (-2.55, 0.60)	-1.1 (-3.66, 1.41); 0.39	-1.3 (-4.78, 2.21); 0.47
	>2	67; 27.9 (7.3)	54; 30.9 (10.9)	128; 29.3 (9.0)	105; 34.7 (12.0)	-2.1 (-4.07, -0.12)		
Memory subscale	≤17	78; 16.1 (3.9)	72; 19.0 (7.0)	187; 15.0 (4.7)	156; 18.3 (8.3)	-0.9 (-2.58, 0.73)	-0.9 (-3.41, 1.52); 0.45	-1.1 (-4.61, 2.39); 0.53
	>17	85; 26.9 (6.6)	63; 29.3 (11.0)	142; 29.9 (7.7)	122; 34.1 (10.8)	-1.8 (-3.67, -0.06)		
Praxis subscale	≤1	89; 18.5 (6.1)	79; 19.9 (7.6)	175; 16.4 (6.4)	153; 18.8 (8.5)	-0.8 (-2.48, 0.77)	-1.2 (-3.62, 1.31); 0.36	-1.7 (-5.25, 1.80); 0.34
	>1	74; 25.7 (7.6)	58; 29.2 (11.4)	154; 27.1 (9.4)	125; 33.1 (11.8)	-2.0 (-3.86, -0.16)		
Number cancellation	≤3	95; 18.6 (5.7)	84; 20.3 (8.1)	186; 17.7 (7.4)	165; 19.9 (9.3)	-0.3 (-1.86, 1.24)	-2.7 (-5.14, -0.21); 0.03	-3.7 (-7.23, -0.21); 0.04
	>3	68; 26.2 (7.9)	53; 29.4 (11.2)	143; 26.3 (10.0)	113; 32.9 (12.2)	-3.0 (-4.89, -1.07)		
EQ-5D-3L (self-reported)	≤0.848	66; 22.0 (8.0)	55; 23.6 (11.6)	156; 20.2 (9.3)	121; 24.0 (11.8)	-1.9 (-3.80, 0.07)	0.9 (-1.62, 3.42); 0.49	1.6 (-2.10, 5.24); 0.40
	>0.848	91; 21.3 (7.4)	79; 24.0 (9.7)	171; 22.4 (9.5)	157; 26.1 (12.7)	-1.0 (-2.58, 0.65)		
QoL-AD (self-reported)	≤39	61; 22.4 (8.0)	52; 24.8 (12.2)	162; 20.5 (9.3)	133; 24.0 (12.0)	-1.2 (-3.12, 0.71)	-0.6 (-3.24, 2.10); 0.68	-0.7 (-4.52, 3.04); 0.70
	>39	78; 21.2 (7.1)	66; 22.9 (9.0)	122; 22.2 (9.4)	110; 25.9 (12.1)	-1.8 (-3.62, 0.06)		
	≤8	56; 22.0 (7.6)	48; 25.8 (11.5)	133; 21.4 (8.9)	114; 25.7 (12.4)	-0.6 (-2.63, 1.52)		

NPI (proxy-reported)	>8	65; 22.4 (8.2)	56; 23.6 (10.0)	109; 22.6 (10.4)	95; 27.3 (12.6)	-2.6 (-4.64, -0.53)	-2.0 (-4.96, 0.89); 0.17	-3.0 (-6.95, 0.95); 0.14
BADLS (proxy-report)	≤11	81; 19.4 (6.3)	72; 21.3 (8.7)	155; 18.6 (7.4)	135; 22.1 (10.9)	-1.1 (-2.82, 0.67)	-1.1 (-3.83, 1.65); 0.44	-1.9 (-5.80, 1.96); 0.33
	>11	60; 25.3 (8.1)	48; 28.2 (11.3)	132; 25.8 (10.6)	107; 31.1 (12.6)	-2.2 (-4.27, -0.06)		

Values are number of participants, mean (standard deviation) unless stated otherwise.

* - 214 participants were classified as compliers.

ADAS-Cog - Alzheimer Disease Assessment Scale cognitive sub-scale; BADL – Bristol Activities of Daily Living Index; IQR – inter-quartile range; NPI – neuropsychological index; QOL-AD - Quality of Life Alzheimer's Disease; sd – standard deviation