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3 **TITLE PAGE**

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

7

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38

39 **Running Header:** Moderators of cognitive outcomes to exercise

40

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

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

47

48

49 **ABSTRACT**

50

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

53

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

55

56 **SETTING:** Community-based gym/rehabilitation centres

57

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

59

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

65

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

68

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

72

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

77

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

79 **INTRODUCTION**

80

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

88 We recently reported a randomised controlled trial investigating the effect of a moderate- to high-
89 intensity aerobic and strength exercise training programme on cognitive impairment at 12 months in
90 494 community-dwelling people with mild to moderate dementia.[6] This targeted known mechanistic
91 pathways in vascular and Alzheimer’s type dementia. At 12-month follow-up, the mean Alzheimer
92 Disease Assessment Scale Cognitive (ADAS-Cog) score increased to 25.2 (standard deviation (SD): 12.3)
93 in the exercise group and 23.8 (SD: 10.4) in the usual care group (indicating worse cognitive
94 impairment in the exercise group).[6] *A priori* subgroup analyses found no evidence for gender,
95 standardised mini-mental state examination (sMMSE) score, prior mobility or type of dementia
96 modifying cognitive function.[6] However, other theoretically plausible subgroups were not tested.
97 Given these results suggest that the intervention could adversely affect cognitive function, this
98 analysis aimed to estimate whether baseline participant variables were able to moderate the effect
99 of the exercise intervention on cognition in patients with mild to moderate dementia.

100

101

102 **METHODS**

103

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

106

107 *Participants and randomisation*

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

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

112

113 *Interventions*

114

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

122

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

125

126 *Outcome Measure*

127

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

136

137 *Statistical Analyses*

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

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

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

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

161

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

164

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

167

168

169 **RESULTS**

170

171 *Cohort Characteristics*

172 From 494 participants randomised, data were available for the primary outcome at 12 months for
173 137/165 (83%) of usual care and 281/329 (85%) of exercise group. Baseline demographic and clinical
174 characteristics for the trial cohort are presented in **Table 1**. These are presented for each subgroup by
175 variable in **Table 2**.

176 *Dispersal of ADAS-Cog Results*

177 **Figure 1** illustrates the change in total ADAS-Cog score from baseline to 12 months for each group.
178 There was a positive change (improved cognitive function) in 49/137 participants (36%) of the usual
179 care group, and 80/281 participants (29%) of the exercise group. There was a negative change
180 (cognitive decline) in 86/137 participants (63%) of the usual care group, and 198/281 participants
181 (71%) of the exercise intervention group.

182 *Principal Analysis*

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

188 Inspection of within-strata changes suggest that cognitive decline was greater for eight variables
189 (**Table 2**). Cognitive decline was greater in those aged over 78 years (-1.7 points; 95% CI: -3.41 to -
190 0.04), those with greater dementia-related behaviours (NPI greater 8 points) at baseline (-2.6 points;
191 95% CI: -4.64 to -0.53) and reduced activities of daily living with a BADLs score of greater than 11
192 points (-2.2 points; 95% CI: -4.27 to -0.06). Cognitive decline was greater for those who lived with
193 others (-1.6 points; 95% CI: -2.96 to -0.24). People with worse cognitive function at baseline in terms
194 of overall function (ADAS-Cog total score greater than 20 points) and all sub-scales (language (greater
195 2 points), memory (greater 17 points), praxis (greater than 1 point) and number cancellation (greater
196 than 3 points) demonstrated greater cognitive decline (**Table 2**).

197

198 **DISCUSSION**

199

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

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

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

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

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

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

247

248 **CONCLUSION**

249

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

254

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287 3) Analysis and interpretation of data: TS, DM, HL, BF, BS, SEL
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296 **REFERENCES**

297

298

299 1. Prince M, Comas-Herrera A, Knapp M, et al. World Alzheimer Report 2016. London, UK,
300 Alzheimer's Disease International, 2016.

301

302 2. Powell T. Health Policy and Dementia. *Curr Psychiatry Rep* 2018;20:4.

303

304 3. Moore KM, Girens RE, Larson SK, et al. A spectrum of exercise training reduces soluble A β in
305 a dose-dependent manner in a mouse model of Alzheimer's disease. *Neurobiol Dis* 2016;85:218-24.

306

307 4. Frederiksen KS, Gjerum L, Waldemar G, et al. Physical activity as a moderator of Alzheimer
308 pathology: a systematic review of observational studies. *Curr Alzheimer Res* 2019;16:362-78.

309

310 5. Dyer SM, Harrison SL, Laver K, et al. An overview of systematic reviews of pharmacological
311 and non-pharmacological interventions for the treatment of behavioral and psychological symptoms
312 of dementia. *Int Psychogeriatr* 2018;30:295-309.

313

314 6. Lamb SE, Sheehan B, Atherton N, et al. Dementia And Physical Activity (DAPA) trial of
315 moderate to high intensity exercise training for people with dementia: randomised controlled trial.
316 *BMJ* 2018;361:k1675.

317

318 7. Atherton N, Bridle C, Brown D, et al. Dementia and Physical Activity (DAPA) -
319 an exercise intervention to improve cognition in people with mild to moderate dementia: study
320 protocol for a randomized controlled trial. *Trials* 2016;17:165.

321

322 8. American Psychiatric Association. Diagnostic and statistical manual of mental disorders
323 (DSM-5®). American Psychiatric Publishing, 2013.

324

325 9. Vertesi A, Lever JA, Molloy DW, et al. Standardized Mini-Mental State Examination. Use and
326 interpretation. *Cam Fam Physician* 2001;47:2018-23.

327

- 328 10. Brown D, Spanjers K, Atherton N, et al. Development of an exercise intervention to improve
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330 registration ISRCTN32612072. *Physiotherapy*. 2015;101:126-34.
331
- 332 11. Mohs RC, Knopman D, Petersen RC, et al. Development of cognitive instruments for use in
333 clinical trials of antidementia drugs: additions to the Alzheimer's Disease Assessment Scale that
334 broaden its scope. *Alz Dis Assoc Dis* 1997;11:13-21.
335
- 336 12. Rockwood K, Fay S, Gorman M. The ADAS-cog and clinically meaningful change in the VISTA
337 clinical trial of galantamine for Alzheimer's disease. *Int J Geriatr Psychiatry* 2010;25:191-201.
338
- 339 13. Vellas B, Andrieu S, Cantet C, et al. Long-term changes in ADAS-cog: what is clinically
340 relevant for disease modifying trials in Alzheimer? *J Nutr Health Aging* 2007;11:338-41.
341
- 342 14. Tak EC, van Uffelen JG, Paw MJ, et al. Adherence to exercise programs and determinants of
343 maintenance in older adults with mild cognitive impairment. *J Aging Phys Act* 2012;20:32-46.
344
- 345 15. Brookes ST, Whitley E, Peters TJ, et al. Subgroup analyses in randomised controlled trials:
346 quantifying the risks of false-positives and false-negatives. *Health Technol Assess* 2001;5:1-56.
347
- 348 16. EuroQol Group. EuroQol-a new facility for the measurement of health-related quality of life.
349 *Health Policy* 1990;16:199-208.
350
- 351 17. Logsdon RG, Gibbons LE, McCurry SM, et al. Assessing quality of life in older adults with
352 cognitive impairment. *Psychosom Med* 2002;64:510-9.
353
- 354 18. Cummings JL, Mega M, Gray K, et al. The neuropsychiatric inventory. Comprehensive
355 assessment of psychopathology in dementia. *Neurology* 1994;44:2308-14.
356
- 357 19. Bucks RS, Ashworth DL, Wilcock GK, et al. Assessment of activities of daily living in dementia:
358 development of the Bristol Activities of Daily Living Scale. *Age and Ageing* 1996;25:113-20.
359
- 360 20. Altman DG, Royston P. The cost of dichotomous continuous variables. *BMJ* 2006;87:9-23.
361

- 362 21. Little RJA, Rubin DB. Statistical Analysis with Missing Data. John Wiley & Sons, Inc, 1986
363
- 364 22. Lam FM, Huang MZ, Liao LR, et al. Physical exercise improves strength, balance, mobility,
365 and endurance in people with cognitive impairment and dementia: a systematic review. *J Physiother*
366 2018;64:4-15.
367
- 368 23. Forbes D, Forbes SC, Blake CM, et al. Exercise programs for people with dementia. *Cochrane*
369 *Database Syst Rev* 2015;4:CD006489.
370
- 371 24. World Health Organisation. Physical activity and adults. Available at:
372 https://www.who.int/dietphysicalactivity/factsheet_adults/en/. Accessed on: 03 April 2020
373
- 374 25. Verma N, Beretvas SN, Pascual B, et al. New scoring methodology improves the sensitivity of
375 the Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog) in clinical trials. *Alzheimers*
376 *Res Ther* 2015;7:64.
377
- 378 26. Della Sala S, Laiacona M, Spinnler H, Ubezio C. A cancellation test:
379 its reliability in assessing attentional deficits in Alzheimer's disease. *Psychol Med* 1992;22:885-901.
380
- 381 27. Halloway S, Schoeny ME, Wilbur J, et al. Interactive effects of physical activity and cognitive
382 activity on cognition in older adults without mild cognitive impairment or dementia. *J Aging Health*
383 2019; In Press.
384
- 385 28. Koščak Tivadar B. Physical activity improves cognition: possible explanations.
386 *Biogerontology* 2017;18:477-83.
387
- 388 29. Wang R, Holsinger RMD. Exercise-induced brain-derived neurotrophic factor expression:
389 Therapeutic implications for Alzheimer's dementia. *Ageing Res Rev* 2018;48:109-21.
390
- 391 30. Olanrewaju O, Kelly S, Cowan A, et al. Physical Activity in Community Dwelling Older People:
392 A Systematic Review of Reviews of Interventions and Context. *PLoS One* 2016;11:e0168614
393
- 394 31. Yeom HA, Keller C, et al. Interventions for promoting mobility in community-dwelling older
395 adults. *J Am Acad Nurse Pract* 2009;21:95-100.
396

397 **FIGURE AND TABLE LEGENDS**

398

399

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

401

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

404

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

407

408

409

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 categorised, 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 stratum: 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

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.



