Does Structured Exercise Improve Cognitive Impairment in People with Mild to Moderate Dementia? A Cost-Effectiveness Analysis from a Confirmatory Randomised Controlled Trial: The Dementia and Physical Activity (DAPA) Trial

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ORIGINAL RESEARCH ARTICLE

Does Structured Exercise Improve Cognitive Impairment in People with Mild to Moderate Dementia? A Cost-Effectiveness Analysis from a Confirmatory Randomised Controlled Trial: The Dementia and Physical Activity (DAPA) Trial

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Abstract

Background Previous studies suggest that physical exercise could slow dementia progression. However, evidence for the cost effectiveness of structured exercise is conflicting and based on small trials.

Objectives The objective of this study was to compare the cost effectiveness of a tailored, structured, moderate- to high-intensity exercise programme versus usual care in people with mild to moderate dementia.

Methods An economic evaluation was conducted from the UK National Health Service and personal social services perspective, based on data from a large randomised controlled trial. The primary clinical outcome was the participant reported ADAS-Cog (Alzheimer's Disease Assessment Scale–Cognitive Subscale) at 12 months. Costs (£; 2014–2015 prices) were collected prospectively over a 12-month follow-up period. A bivariate regression of costs and quality-adjusted life-years (QALYs), with multiple imputation of missing data, was conducted with the view to estimating the incremental cost per QALY gained and the incremental net monetary benefit (INMB) associated with the exercise programme plus usual care versus usual care. Sensitivity analyses were undertaken to assess the impact of uncertainty surrounding aspects of the economic evaluation, and pre-specified subgroup analyses explored heterogeneity in the cost-effectiveness results.

Results Participants ($n=494$) were randomised to exercise plus usual care or usual care only. By 12 months the mean ADAS-Cog score had worsened slightly to 25.2 (standard deviation [SD] 12.3) in the exercise arm and 23.8 (SD 10.4) in the usual care: difference − 1.4, 95% confidence interval (CI) − 2.6 to − 0.2 ($p=0.03$). The mean (standard error [SE]) costs over 12 months for experimental versus control was £5945 (US$7856) versus £4597 (US$6574), respectively; (difference: £1347 [$1926]; $p=0.0426$). Mean (SE) QALY estimates were 0.787 (0.012) versus 0.826 (0.019), respectively ($p=0.090$). The probability that the exercise programme is cost effective was < 1% across cost-effectiveness thresholds. INMBs ranged between –£2601 (US$3719) and £2158 (US$3086) at cost-effectiveness thresholds between £15,000 (US$21,450) and £30,000 (US$42,900) per QALY. The cost-effectiveness results remained robust to several sensitivity and subgroup analyses.

Conclusions Building on the clinical results of the trial, which showed that the structured exercise programme evaluated does not slow cognitive impairment in people with mild to moderate dementia, this economic evaluation shows that the programme is not cost effective.

DAPA Trial Group members are listed in Acknowledgement section.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s41669-018-0097-9) contains supplementary material, which is available to authorized users.

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Key Points for Decision Makers

This study is the largest randomised controlled trial to date that evaluates the cost effectiveness of structured exercise in in people with dementia.

Structured exercise is shown not to be cost effective for people with dementia.

Patients became physically fitter due to exercise; these benefits did not translate into improvements in important cognitive outcomes.

1 Introduction

Dementia is a syndrome characterised by acquired, progressive deterioration in memory, general cognitive function, self-care and personality. It affects mainly older people. Dementia prevalence in developed countries approximately doubles in successive 5-year age groups between 65 and 99 years, from under 1% for 65- to 69-year-olds to about 35% in 95- to 99-year-olds [1]. Approximately 60% and 20% of dementia cases in developed countries are caused by Alzheimer's disease and vascular dementia, respectively [2], whilst mixed Alzheimer's/vascular dementia and dementia with Lewy bodies are other common causes. In the UK, there are approximately 670,000 dementia sufferers [3].

Although dementia prevalence has fallen in Western Europe and the USA [4, 5], the worldwide economic burden of dementia remains high at US$815 billion [6]. In the USA, this economic burden is estimated to be at least US$157 billion [7]. In Europe, it is approximately €250 billion (US$268 billion) [8, 9], £23 billion [10] (US$35 billion) of which falls on the UK health services. The global cost is expected to rise to US$2 trillion by 2030 [6]; hence, reducing it is important to healthcare systems worldwide. Moreover, common drug treatments offer modest efficacy with average annual acquisition costs, ranging from £948 (US$1197) to £996 (US$1423) (56 tablet pack, depending on dose) for rivastigamine and galantamine, respectively [11, 12], excluding costs associated with toxicity-related over-exposure (high dosing) or drug interactions [13]. The probability of cost effectiveness of these drug treatments does not exceed 20% at cost-effectiveness thresholds as high as £40,000 per additional quality-adjusted life-year (QALY) [14].

Current (drug) interventions aim to reduce risk and/or alleviate symptoms of, rather than cure, dementia. Some (mechanistic) studies have shown positive associations between physical activity and cognition [15] in humans. Structured exercise has been shown to offer benefit to dementia sufferers in several previous epidemiological studies [16–18]. In clinical studies, however, no confirmatory evidence on the effectiveness of exercise on dementia symptoms has been reported. This may be due to several factors associated with study design, heterogeneity in the populations, small sample sizes and exercise intensity. Moreover, evidence for the cost effectiveness of exercise in people with dementia is limited and based on small trials [19, 20].

We therefore present the results from a cost-effectiveness analysis of a high-intensity structured exercise intervention delivered in the context of the largest confirmatory randomised controlled trial (RCT) reported to date.

2 Methods

2.1 Trial Background

The DAPA (Dementia and Physical Activity) RCT was a multicentre, pragmatic RCT. Individuals with a clinically confirmed diagnosis of dementia in accordance with the *Diagnostic and Statistical Manual, 4th Edition* (DSM-IV), and a standardised Mini-Mental State Examination (sMMSE) score of > 10, were recruited from 15 regions across England between February 2013 and June 2015. Participants were randomised (2:1 ratio) to either a moderate- to high-intensity, tailored structured exercise programme or usual practice.

The primary clinical outcome was the participant-reported ADAS-Cog (Alzheimer's Disease Assessment Scale–Cognitive Subscale) at 12 months. A total of 375 participants were required to detect a difference of 2.45 ADAS-Cog points (standardised effect of 0.31) in the ADAS-Cog (80% power, 5% type I error). Further details of the trial are reported elsewhere [21, 22].

2.2 Interventions

2.2.1 Exercise (Experimental)

The exercise intervention was divided into two parts: a supervised component (4 months) and an unsupervised component lasting an additional 8 months. The supervised component comprised a pre-exercise assessment and twice-weekly exercise supervision by trained physiotherapists and exercise assistants of 60–90 min duration for 4 months with a target of at least 50 min of unsupervised activity at moderate intensity, to achieve a total of 150 min per week. The exercises classes involved a combined aerobic and resistance training schedule at moderate to hard intensity, delivered in groups of up to eight participants.

2.2.2 Usual Care (Control)

All participants received usual care consistent with the National Institute for Health and Care Excellence (NICE) clinical guidance [23]. This comprised counselling for carers and families, clinical assessment, prescription of symptomatic treatments and brief advice about physical activity [24, 25]. Treatment was determined by the participants' physicians on the basis of clinical need and was monitored through the study period.

2.3 Overview of Economic Evaluation

The economic evaluation was designed as a cost-utility analysis with the cost effectiveness of the exercise intervention, compared with usual care, expressed in terms of incremental cost per QALY gained. The primary analysis was undertaken from the perspective of the UK National Health Service (NHS) and Personal Social Services (PSS), as recommended by NICE methodological guidance for technology appraisals and additionally from a societal perspective for the purposes of a sensitivity analysis [26]. A 12-month time horizon for the economic evaluation was used (12-month follow-up of RCT), and therefore no discounting was required.

2.4 Cost of the Exercise Programme

The costs relating to delivering the exercise programme, inclusive of training, delivery of group sessions, equipment (e.g. belts, weights, exercise bike), monitoring activities, follow-up, administrative activities, telephone contacts, supervision activities, travel costs and venue hire costs were estimated using weekly activity logs completed by physiotherapists and exercise assistants. Cost data were combined with attendance data to derive estimates of mean cost per session per attending participant for each group within each site.

2.5 Measurement of Broader Resource Use

Broader health and personal social service and broader societal resource inputs (for the purposes of a sensitivity analysis) were collected (through interviews) at baseline and 6 and 12 months post-randomisation using a modified version of the Client Services Receipt Inventory (CSRI; version 1.0) [27, 28]. Resource use data included use of sheltered housing/care home accommodation, hospital and day-care services, community-based health and social care, and aids and equipment. Details of travel costs (borne by trial participants or family members or friends) due to the trial participants' health status or contacts with health or social services were collected. Medication costs were derived from dose frequency and duration.

2.6 Valuation of Resource Use

Resource inputs were valued using primary research (e.g. participant travel costs, participant time taken off work) and data collated from secondary sources, with the valuation of the latter informed by national methodological guidance (Electronic Supplementary Material Appendix Table 1) [26].

Staff inputs associated with the delivery of the exercise programme were determined from hourly unit costs for each Agenda for Change band [29]; these included staff salaries, qualification costs, employer on-costs and associated revenue and capital overheads. Travel costs (for each mile) were determined from the Automobile Association (AA) [30] and the Department for Transport Public Service Vehicle Survey [31]. Hospital inpatient admissions were valued using NHS Reference Costs trusts schedules [32]. Other hospital-based costs were valued using national tariffs [29, 32]. Community health and social care resource use was valued using secondary sources [29]. Participant-level costs for medication use were valued using Health and Social Care Information Centre (HSCIC) drug costs (2015) [11]. Gender-specific median earnings data were derived from self-reported work status information and used to estimate the costs of time taken off work (by family members/carers or participants). Other family-borne costs were also determined. The NHS Hospital and Community Health Services Pay and Prices Index was used to inflate/deflate costs where necessary to 2014–2015 prices (£ sterling) [33].

2.7 Health-Related Quality of Life: Health Utilities and QALYs

Health-related quality of life (HRQoL) of participants was assessed by both participants and carers using the EuroQol EQ-5D-3L [34] at baseline and 6 and 12 months post-randomisation for generating QALY profiles. The EQ-5D-3L consists of a descriptive system, which defines HRQoL across five dimensions: 'mobility', 'self-care', 'usual activities', 'pain/discomfort' and 'anxiety/depression'. Responses in each dimension are scored as no problems (1), some or moderate problems (2) and severe or extreme problems (3). The UK time trade-off tariff was applied to each set of responses to generate an EQ-5D-3L utility score for each trial participant [34]. Resulting utility scores range from − 0.59 to 1.0, with 0 representing death and 1.0 representing full health; values below 0 are indicative of health states worse than death. The visual analogue scale (VAS) of the EQ-5D-3L, ranging from 100 (best imaginable health state) to 0 (worst imaginable health state), was included in the assessments. QALYs were calculated as the area under the baseline-adjusted utility curve using linear interpolation between baseline and 6 and 12 months, with the adjustment

process accounting for variation in baseline utility values [35].

2.8 Missing Data

Multiple imputation (MI) using the method of chained equations (MCMC) was used for the base-case analysis to impute missing resource use and HRQoL data [36], taking into account covariates including baseline costs, baseline utilities, age, gender and baseline MMSE score ($<20; \geq 20$). Mean matching using predictive methods was used to improve estimates of imputed values since normality could not be assumed. Each imputed dataset was analysed independently using model-based approaches; estimates were pooled to generate mean and variance estimates of costs and QALYs using Rubin's rule to capture within and between variances for imputed samples [37]. Information loss from finite imputation sampling was minimised using 20 datasets, resulting in minimal loss of efficiency (<0.5%) [38]. Since the fraction of information missing was reasonably low, 20 imputation sets were considered adequate. Imputed and observed values were compared to establish that imputation did not introduce bias into subsequent estimation [38].

2.9 Cost-Effectiveness Analyses

Mean resource use, cost and utility values were compared between groups using two sample *t*-tests. Differences between groups, along with confidence intervals (CIs) were estimated using non-parametric bootstrap estimates (10,000 replications) [26]. Seemingly unrelated regression (SUR) methods that account for the correlation between costs and outcomes were used to estimate mean incremental costs and QALYs whilst adjusting for covariates (baseline costs, baseline utilities, age, gender, and baseline MMSE score ($<20; \geq 20$). Non-parametric bootstrap methods were used to generate the joint distributions of costs and outcomes to populate the cost-effectiveness plane. Bias-corrected non-parametric bootstrapping was used so that the sample correlation structure was preserved.

The incremental cost-effectiveness ratio (ICER) was estimated as the difference between groups in mean total costs divided by the difference in mean total QALYs. Mean ICER values were compared against cost-effectiveness threshold values [39] ranging between £15,000 (US$21,450) and £30,000 (US$42,900) per QALY using 2015 purchasing power parities (£1 = US$1.43) [33], thereby encompassing threshold values recommended by NICE. The cost-effectiveness thresholds provide an indication of society's willingness to pay for an additional QALY; lower ICER values than the threshold could be considered cost effective for use in the UK NHS. The incremental net monetary benefit (INMB) of switching from usual care to an exercise programme was also reported. The INMB describes the resource gain (or loss) when investing in a new intervention when resources can be used elsewhere at the same cost-effectiveness threshold. Cost-effectiveness acceptability curves (CEACs) showing the probability of the exercise programme being cost effective over the range of cost-effectiveness thresholds were generated. All analyses were conducted in SAS® version 9.4 (SAS Institute, Cary, NC, USA) on a Microsoft Windows (Microsoft Corp., Redmond, WA, USA) platform.

2.10 Sensitivity and Subgroup Analyses

Several pre-specified sensitivity analyses were undertaken to assess the impact on the base-case economic evaluation. These included a complete cases analysis, adopting a wider societal perspective that included costs incurred by all sectors of the economy, recalculating QALYs using carer-reported EQ-5D-3L values, recalculating the average cost per participant per exercise session by taking into account practitioner travel costs, varying the cohort size for the exercise programme between the lowest ($n = 3$) and highest ($n = 10$) number of participants attending across all exercise groups, and setting the venue hire costs to zero (on the assumption that delivery of the exercise programme in routine UK NHS settings, rather than community venues, may be associated with zero opportunity costs). Pre-specified subgroup analyses were conducted by gender (male, female) and baseline MMSE score ($<20, \geq 20$).

3 Results

3.1 Study Population and Clinical Results

From the 494 participants randomised (329 to the exercise programme and 165 to usual care), complete baseline information was available for 488 participants (326 for exercise and 162 for control) for the base-case economic evaluation. Between 91 and 99% and 91 and 98% of health resource use data were complete at baseline for the exercise and usual care groups, respectively (Table 1 and Electronic Supplementary Material Appendix Table 2).

Complete QALY profiles were available for 435 (88%) participants based on the participant-reported EQ-5D-3L (84% for the carer-reported EQ-5D-3L). There was no clinical benefit based on the primary ADAS-Cog outcome: the mean ADAS-Cog was 25.2 (standard deviation [SD] 12.3) compared with 23.8 (SD 10.4) for exercise versus usual care, with an adjusted mean difference of –1.4 (95% CI − 2.6 to − 0.2; $p = 0.026$) [22] (higher scores reflect worse outcomes for ADAS-Cog). Further details of the clinical results of the trial can be found elsewhere [22].

Table 1 Summary of economic data completion and demographics

Economic data/demographic characteristic	Exercise ($n=329$)	Usual care ($n=165$)
Age (years) [mean (SD)]	76.9 (7.9)	78.4 (7.6)
Gender (male) [*n* (%)]	195 (59.3)	106 (64.2)
Ethnicity [*n* (%)]		
White	321 (97.6)	157 (95.2)
Other	8 (2.4)	8 (4.8)
Health resource use (CSRI) completion (minimum–maximum [%])		
Baseline	91–98	91–99
6 months	76–86	84–91
12 Months	75–82	78–85
EQ-5D-3L utility (participant) completion (%)		
Baseline	98	96
6 months	88	83
12 Months	78	75
QALY (participants) completion[a]	88	87

CSRI Client Services Receipt Inventory, *QALY* quality-adjusted life-year, *SD* standard deviation

[a]A full QALY profile estimable between baseline and 12 months

3.2 Cost of Intervention

The intervention cost components are reported under four main headings: (i) staff costs, inclusive of training activities, planning, direct delivery, administrative activities, meetings with professionals, telephone calls and supervision activities associated with group delivery; (ii) travel costs, based on distances travelled by practitioners by mode of transport; (iii) venue hire costs; and (iv) equipment and other costs for each site, including cost of belts, stopwatches, timers, cones, lap counters, CDs, stationery (e.g. pens, erasers) and trial manuals, associated with group delivery. Total intervention costs are also presented within each group within each site (Electronic Supplementary Material Appendix Table 3). These varied between £4444 (US$6355) (Worcester, cohort 53) and £11,342 (US$16,219) (Wolverhampton, cohort 50). The average costs per exercise session per participant varied from about £29 (US$41) (Amersham, cohort 4), to £108 (US$154) (Atrium, cohort 9).

3.3 Broader Resource Use

Broader resource use values are presented for participants with complete data by trial allocation, resource use category and study period (Electronic Supplementary Material Appendix Table 4).

Amongst participants with complete resource use data, the most frequent health resource inputs were general practitioner (GP) visits, hospital stays, practice nurse visits and community psychiatrist contacts. On average, there were no statistical differences in broader health resource use between groups (Electronic Supplementary Material Appendix Table 4). The mean (standard error [SE]) number of GP contacts per participant over 12 months was 1.8 (0.14) in the exercise arm compared with 1.7 (0.27) in the usual care arm ($p=0.876$). Community mental healthcare services, primarily through psychiatric support, were used by a smaller proportion of participants in the exercise group at 12 months (10% [28/280] vs. 14% [19/136]; $p=0.224$). No noticeable differences in terms of other healthcare resource use were observed between baseline and 12 months for hospital stays, practice nurse visits and community psychiatrist contacts. Resource use frequencies in other categories were low; hence, meaningful comparisons could not be easily made (Electronic Supplementary Material Appendix Table 4).

3.4 Economic Costs

With the exception of the cost of the exercise intervention, there were no statistically significant differences between the trial groups in any cost category between randomisation and 12 months (Table 2).

The mean cost of the exercise programme over the entire follow-up period was £1269 (US$1815). Mean total NHS and personal social service costs, inclusive of the cost of the intervention, were £5945 (US$8501) in the intervention arm compared with £4597 (US$6534) in the control arm, generating a mean cost difference of £1347 (US$1926) (bootstrap 95% CI £8–2136 [US$11–3054]; $p=0.0426$). Over the entire follow-up period, and for participants with complete data, mean total societal costs, inclusive of the cost of the intervention, were £6063 (US$8670) in the intervention arm compared with £4761 (US$6808) in the control arm, generating a mean cost difference of £1301 (US$1860) (bootstrap 95% CI £3–2096 [US$4–2997]; $p=0.0479$).

3.5 Health-Related Quality of Life Outcomes

For complete cases, there were no statistically significant differences in participant- or carer-reported EQ-5D-3L utility or EQ-5D VAS scores between the exercise and usual care groups. The mean (SE) participant reported QALY estimate was 0.787 (0.012) versus 0.826 (0.019) ($p=0.090$) for exercise versus usual care (Table 3); this was 0.758 (0.014) versus 0.782 (0.020) for the carer-reported EQ-5D-3L ($p=0.330$).

3.6 Cost-Effectiveness Results: Base-Case Analysis

The baseline economic evaluation, using imputed attributable costs and QALYs with covariate adjustment, resulted in mean total costs of £5580 (US$7974) in the exercise group compared with £3917 (US$5601) in the usual care

Table 2 Economic costs for complete cases by trial allocation, study period and cost category (£; 2014–2015 prices): randomisation to 12 months ($n=416$ total; $n=280$ exercise and $n=136$ usual care)

Cost category by period	Exercise [mean (SE)]	Usual care [mean (SE)]	Mean difference	p-value[a]	Bootstrap 95% CI[b]
NHS/PSS costs					
Patient accommodation	187.6 (58.02)	54.4 (30.16)	133.2	0.0513	− 6.9 to 210.8
Hospital services	2019.3 (466.80)	1827 (320.04)	192.3	0.7342	− 1001.9 to 858.1
Day-care services	33.9 (4.82)	49.2 (10.25)	− 15.3	0.1685	− 36.9 to 1.12
General community health services	366.3 (38.25)	347.6 (27.88)	18.7	0.6438	− 62.3 to 64.9
Community mental health services	163.6 (27.08)	150.2 (23.81)	13.4	0.7108	− 62.2 to 56.3
Social care services	647 (123.9)	759.9 (190.09)	− 112.9	0.6190	− 565.3 to 169.3
Equipment, adaptations/repairs	1.9 (0.62)	14.5 (10.23)	− 12.6	0.2092	− 30.6 to 1.74
Participant travel[c]	5.7 (0.58)	7 (1.01)	− 1.3	0.2651	− 3.6 to 0.16
Concomitant/prescription medications	1046.2 (78.66)	1067.4 (161.72)	− 21.2	0.9081	− 372.3 to 209.4
Other	204.5 (37.86)	321 (184.50)	− 116.5	0.5366	− 466.4 to 140.4
Total (NHS/PSS)	4676.2 (507.66)	4597.3 (444.35)	78.7	0.9066	− 1336.7 to 880.3
Broader societal costs					
Privately provided general community health services	9.1 (4.32)	3.4 (2.33)	5.7	0.2431	− 4.8 to 11.4
Privately provided mental health services	19.6 (5.35)	103.5 (73.61)	− 83.9	0.2562	− 216.5 to 21.1
Participant equipment	8.5 (4.12)	7.4 (4.77)	1.1	0.8617	− 11.8 to 8.8
Participant travel[d]	2.1 (0.57)	3.4 (0.97)	− 1.3	0.2656	− 3.6 to 0.16
Time off work (h)	13.8 (3.92)	10.3 (4.24)	3.5	0.5417	− 8.3 to 10.4
Time off work (days)	65.2 (19.19)	35.8 (12.46)	29.4	0.2001	− 19.1 to 56.3
Total broader societal costs	118.3 (20.55)	163.7 (20.01)	− 45.4	0.0594	− 104.1 to 1.4
Total (societal costs)	4794.3 (510.66)	4761.0 (447.24)	33.3	0.9609	− 1390.5 to 838.8
Intervention costs	1268.7 (29.56)				
Total PSS/NHS including intervention costs	5944.9 (491.75)	4597.3 (444.35)	1347.4	0.0426	8.2 to 2135.7
Total societal including intervention costs	6063.0 (494.08)	4761.1 (447.24)	1301.9	0.0479	2.8 to 2095.5

CI confidence interval, *NHS* National Health Service, *PSS* personal social services, *SE* standard error

*Statistically significant at the 2-sided 5% level

[a]p value calculated using student's t-test, 2-tail unequal variance

[b]Non-parametric bootstrap estimation using 10,000 replications, bias corrected

[c]Participant travel consisted of ambulance or NHS-supported travel

[d]Participant travel consisted of private transport costs (e.g. private taxi)

group, a mean incremental cost of £1663 (US$2378). The mean incremental cost-effectiveness of the exercise intervention was estimated to be − £74,227 (− US$106,145) per QALY, i.e. on average, the experimental intervention was associated with a higher cost and a lower effect and was dominated in health economic terms. The associated mean INMB at cost-effectiveness thresholds of £15,000, £20,000 and £30,000 per QALY were − £2158 (− US$3086), − £2306 (− US$3298) and − £2601 (− US$3719), respectively (Table 4). The base-case mean INMB was < 0, suggesting that the exercise group would result in an average net economic loss of about £2158 (US$3086) (INMB = − £2,158, 95% CI − £3455 to − £969 [− US$4941 to − US$1386]). The cost-effectiveness plane (Fig. 1) shows that the vast majority of the ICER values lie in the north-west quadrant.

The subsequent probability of cost effectiveness is close to zero (Fig. 1), i.e. if decision-makers are willing to pay between £15,000 and £30,000 for an additional QALY, the probability that the exercise intervention is cost effective is < 1% (Table 4).

3.7 Sensitivity Analyses

The probability that the exercise intervention is cost effective remained relatively static (< 1%) for the majority of the sensitivity analyses (complete cases, societal costs, carer-reported EQ-5D, inclusion of practitioner travel costs, changes in the number of participants per cohort to the lowest number observed). When venue hire costs were excluded and the number of participants per cohort was set at the highest number observed across all groups, the probability that the

Table 3 Cost-effectiveness, cost/quality-adjusted life-year (£; 2014–2015): exercise programme compared to usual care

	Incremental cost (95% CI)	Incremental QALYs (95% CI)	ICER[a,b]	Probability of cost effectiveness			INMB		
				p^c	p^d	p^e	INMB[a,c]	INMB[a,d]	INMB[a,e]
Base case (NHS/PSS perspective)									
Imputed attributable costs and QALYs, covariate- and baseline-adjusted EQ-5D utility score	1663 (120 to 3207)	− 0.0220 (− 0.0621 to 0.0181)	Dominated	0.0011	0.0012	0.0014	− 2158 (− 3455 to − 969)	− 2306 (− 3678 to − 1041)	− 2601 (− 4128 to − 1176)
Sensitivity analyses									
1. Complete cases attributable costs and QALYs, and baseline-adjusted EQ-5D utility score	1549 (458 to 2764)	− 0.0254 (− 0.0592 to 0.0084)	Dominated	0.0044	0.0044	0.0050	− 1943 (− 3238 to − 756)	− 2071 (− 3420 to − 828)	− 2325 (− 3823 to − 922)
2. Imputed societal attributable costs and QALYs, covariate- and baseline-adjusted EQ-5D utility score	1574 (6 to 3123)	− 0.0220 (− 0.0621 to 0.0181)	Dominated	0.0079	0.0079	0.0068	− 1710 (− 2896 to − 503)	− 2233 (− 3789 to − 777)	− 2412 (− 3936 to − 972)
3. Imputed attributable costs and QALYs, covariate- and baseline-adjusted carer-reported EQ-5D utility score	1663 (120 to 3207)	− 0.00665 (− 0.0453 to 0.0320)	Dominated	0.0026	0.0027	0.0044	− 1867 (− 3094 to − 757)	− 1917 (− 3182 to − 757)	− 2017 (− 3380 to − 738)
4. Imputed attributable costs and QALYs, covariate- and baseline-adjusted EQ-5D utility score including practitioner travel costs	1971 (959 to 3122)	− 0.0220 (− 0.0621 to 0.0181)	Dominated	0	0.0010	0.0025	− 2264 (− 3439 to − 1124)	− 2379 (− 3625 to − 1178)	− 2610 (− 4034 to − 1216)
5. Imputed attributable costs and QALYs, covariate- and baseline-adjusted EQ-5D utility assuming cohort size ($n = 3$)	2773 (2458 to 2954)	− 0.0220 (− 0.0621 to 0.0181)	Dominated	0	0	0.0001	− 3055 (− 3327 to − 2790)	− 3172 (− 3454 to − 2891)	− 3406 (− 3723 to − 3085)
6. Imputed attributable costs and QALYs, covariate- and baseline-adjusted EQ-5D utility assuming cohort size ($n = 10$)	983 (669 to 1165)	− 0.0220 (− 0.0621 to 0.0181)	Dominated	0.0495	0.0486	0.0511	− 1265 (− 1538 to − 1000)	− 1382 (− 1663 to − 1102)	− 1616 (− 1931 to − 1294)
7. Imputed attributable costs and QALYs, covariate- and baseline-adjusted EQ-5D utility score, excluding venue hire costs	1203 (–61 to 2240)	− 0.0220 (− 0.0621 to 0.0181)	Dominated	0.0250	0.0260	0.050	− 1417 (− 2698 to − 219)	− 1543 (− 2892 to − 286)	− 1796 (− 3297 to − 364)
Subgroup analyses (gender and MMSE score)									
Male: Imputed attributable costs and QALYs, covariate- and baseline-adjusted EQ-5D utility score	1383 (23 to 3068)	− 0.0263 (− 0.049 to 0.027)	Dominated	0.0461	0.0486	0.0608	− 1631 (− 3346 to − 33)	− 1688 (− 3469 to − 12)	− 1802 (− 3784 to − 105)
Female: Imputed attributable costs and QALYs, covariate- and baseline-adjusted EQ-5D utility score	1511 (− 74 to 3126)	− 0.0215 (− 0.087 to 0.0127)	Dominated	0.0012	0.0016	0.0030	− 2140 (− 3744 to − 568)	− 2239 (− 4028 to − 499)	− 2440 (− 4632 to − 322)
Baseline MMSE < 20: Imputed attributable costs and QALYs, covariate- and baseline-adjusted EQ-5D utility score	1206 (804 to 1385)	− 0.00204 (− 0.0135 to 0.00935)	Dominated	0.0318	0.0326	0.0375	− 1128 (− 1470 to − 779)	− 1139 (− 1519 to − 753)	− 1161 (− 1624 to − 696)

Table 3 (continued)

	Incremental cost (95% CI)	Incremental QALYs (95% CI)	ICER[a,b]	Probability of cost effectiveness			INMB		
				p^c	p^d	p^e	INMB[a,c]	INMB[a,d]	INMB[a,e]
Baseline MMSE ≥ 20: Imputed attributable costs and QALYs, covariate- and baseline-adjusted EQ-5D utility score	1951 (1585 to 2331)	− 0.0334 (− 0.0415 to 0.0253)	Dominated	0.0090	0.0011	0.0021	− 2453 (− 2856 to − 2066)	− 2621 (− 3042 to − 2216)	− 2955 (− 3415,− 2505)

CI confidence interval, *ICER* incremental cost-effectiveness ratio, *INMB* incremental net monetary benefit, *MMSE* Mini-Mental State Examination, *NHS* National Health Service, *PSS* personal social services, *QALY* quality-adjusted life-year

[a]CIs based on 10,000 simulations. Each simulation based on model-based means adjusted for baseline utility, baseline MMSE, gender, age and region, where appropriate, unless stated otherwise (12% data missing/imputed for QALYS and 5% for costs)

[b]Dominated indicates average costs were less and average benefit greater for the usual care group

[c]Probability cost effective or net monetary benefit if cost-effectiveness threshold is £15,000/QALY

[d]Probability cost effective or net monetary benefit if cost-effectiveness threshold is £20,000/QALY

[e]Probability cost effective or net monetary benefit if cost-effectiveness threshold is £30,000/QALY

Table 4 Participant- and carer-reported EQ-5D-3L quality-adjusted life-years (complete cases)

	QALY (EQ-5D-3L participant)		QALY (EQ-5D-3L carer)	
	n	Mean (SE)	*n*	Mean (SE)
Exercise	294	0.787 (0.012)	279	0.758 (0.014)
Usual care	141	0.826 (0.019)	137	0.782 (0.020)
Mean difference[a]		− 0.039		− 0.024
p-value (95% CI)		0.090 (− 0.083 to 0.0061)		0.330 (− 0.073 to 0.0324)

CI confidence interval, *QALY* quality-adjusted life-year, *SE* standard error

[a]Exercise versus usual care

exercise intervention is cost effective remained below 5%. The average INMB was unlikely to be positive as all upper 95% confidence limits were below zero (Table 4 and Fig. 2).

3.8 Subgroup Analyses

The four pre-planned subgroup analyses showed no evidence that gender or the baseline MMSE score has a significant effect on the cost effectiveness of the exercise programme (Table 4 and Fig. 3).

4 Discussion

This trial-based economic evaluation revealed that a moderate- to high-intensity aerobic and strength exercise programme delivered in community settings is not cost effective compared with usual care for adults with mild to moderate dementia. The INMB estimate was negative, a finding that remained robust to several sensitivity and subgroup analyses. The strong evidence against our structured exercise programme developed for people with mild to moderate dementia generated by this trial-based economic evaluation is unlikely to be altered by extrapolation of cost effectiveness over a longer time horizon. Although it may be possible that there are cumulative or learning effects for which the benefits of the structured exercise programme may manifest over the longer term, follow-up after 12 months did not appear to point to this [22].

The main reason for lack of cost effectiveness of the exercise intervention appears to stem from limited clinical benefit as well as it being more costly. We present a rigorous evaluation of the costs involved (exceeding on average £100 per participant per session). This cost is higher than other experimental exercise interventions reported elsewhere [19]. However, this is likely to be due to the inclusion of more intensive support by trained physiotherapists and exercise assistants than other programmes as well as

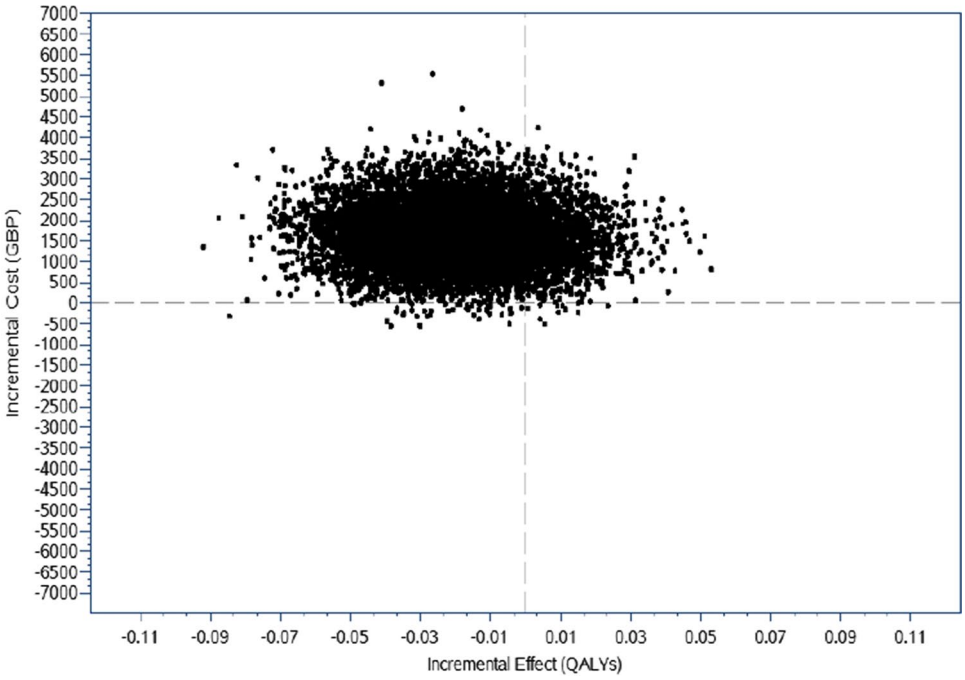

Fig. 1 Cost-effectiveness plane. *GBP* British pounds, *QALYs* quality-adjusted life-years

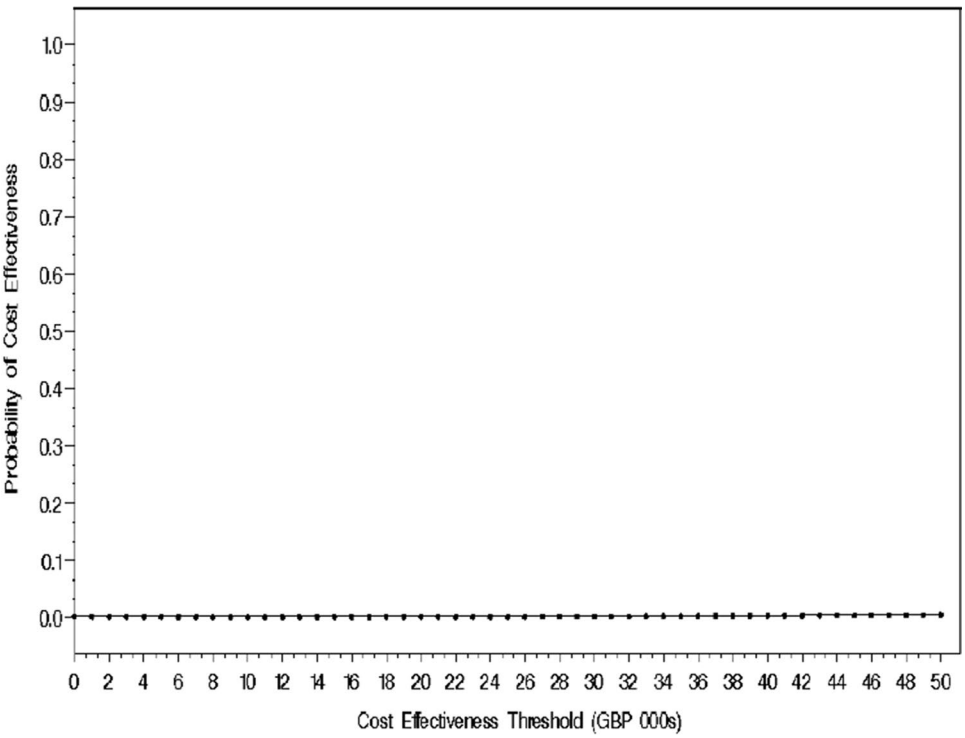

Fig. 2 Cost-effectiveness acceptability curve. *GBP* British pounds

several other cost components such as equipment and use of site in our calculation of the cost of the intervention. Although patients became physically fitter due to exercise [21], these benefits did not translate into improvements in mobility and functional activities that may have required demonstrating improved motor re-learning or cognitive outcomes. It is possible that carers are reluctant to encourage dementia sufferers to re-establish functional activities through fear of injury, although this remains to be elucidated through further research. Consequently, in the absence of any effect in either the primary clinical outcome or the EQ-5D-3L-based QALY, usual care was dominant in health economic terms. Unless exercise programmes are demonstrated to result in downstream cost

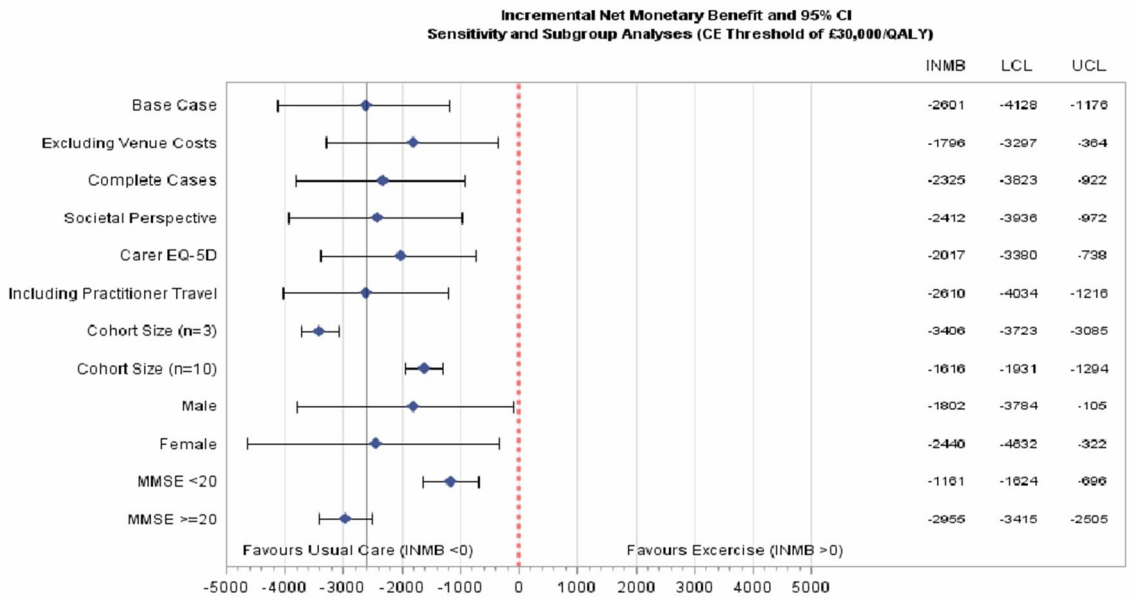

Fig. 3 Sensitivity and subgroup analyses. *CE* cost effectiveness, *CI* confidence interval, *INMB* incremental net monetary benefit, *LCL* lower 95% confidence interval, *MMSE* Mini-Mental State Examination, *QALY* quality-adjusted life-year, *UCL* upper 95% confidence interval

savings and/or improvements in cognitive or HRQoL outcomes, they are unlikely to be cost effective in resource-constrained systems.

There is limited evidence for cost effectiveness of organised high-intensity exercise interventions in dementia patients reported in the broader literature. This cost-effectiveness analysis using participant-level data is based on the largest RCT of its kind reported to date. The results from our analyses are consistent with a recent economic evaluation of exercise therapy for behavioural and psychological symptoms of dementia [19]. In that smaller RCT ($n = 131$ subjects), exercise therapy was not cost effective. Our larger trial offers a confirmatory conclusion in this regard. In contrast, another smaller ($n = 40$) trial [20] suggests that community-based exercise programmes confer cognitive and physical benefits with potential to show cost effectiveness, but this remains to be substantiated in larger well-controlled studies.

The main strengths of this analysis are that the trial was prospectively designed for a cost-effectiveness analysis using individual-level data to reach a confirmatory conclusion with respect to exercise training as an intervention in people with dementia. There were, however, several limitations to this cost-effectiveness analysis. Firstly, QALYs were based on utility measurements at just two timepoints post-randomisation. Although the trial did not yield benefits, the assumption of linearity of HRQoL between data collection points is uncertain and becomes more uncertain when missing data are present.

Secondly, despite the longitudinal nature of the study, resource use was retrospectively recalled by trial participants and carers, which is likely to have resulted in some recall bias; although the bias is likely to have been similar between randomised arms. Thirdly, a smaller pilot or phase II trial may have been useful in identifying the critical costs that drive cost effectiveness. Instead, data for a broad spectrum of cost categories were collected which, on average, had little impact on the ICER. Many costs items did not occur (Electronic Supplementary Material Appendix Tables 3 and 4) and a reduced form of the CSRI in this setting may be advisable with a focus on the largest and most relevant costs. In addition, the CSRI in several places could be improved as it leads to many categories of 'other' costs that are time consuming for data management. Many of these costs had little impact on the results. Sensitivity analyses, for example, showed the cohort size as the most influential factor on the INMB and not some of the cost components incorporated into the analysis.

Finally, the 95% CI for the incremental QALYs does not exclude the possibility of a small QALY benefit (the upper 95% CI is greater than zero; Table 4). However, the upper limit of these intervals from the sensitivity analyses is less than about 0.03 (e.g. for the carer-reported EQ-5D-3L). Hence, for an observed base-case incremental cost of £1683 (US$2407), the ICER is very unlikely to be cost effective even in the most optimistic scenario (i.e. £1683/0.03, an ICER of £56,100 [US$80,223] per QALY in the best case).

5 Conclusion

Data collected in the DAPA trial provides strong evidence that our structured, moderate- to high-intensity exercise

programme, in addition to usual care, is unlikely to be cost effective for mild to moderate dementia sufferers when compared with usual care alone.

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Author Contributions Dr Iftekhar Khan (Research Fellow, Health Economist): member of the Trial Management Group (TMG), responsible for the economic analysis of the trial, writing and reviewing of report. Prof Stavros Petrou (Professor of Health Economics, co-applicant): protocol development, member of the TMG, responsible for the economic analysis of the trial, writing and reviewing of report. Dr Dipesh Mistry (Research Fellow, Trial Statistician): member of the TMG, responsible for the statistical analysis of the trial, writing and reviewing of report. Kamran Khan (Research Associate, Health Economist): former member of the TMG, responsible for the economic analysis of the trial, writing and reviewing of report. Dr Ranjit Lall (Principal Research Fellow, co-applicant): developed the protocol, member of the TMG, responsible for the statistical analysis of the trial, writing and reviewing of report. Dr Bart Sheehan, (Consultant in Psychological Medicine): study design, clinical responsibility, writing and reviewing of report. Professor Sarah Lamb (Professor of Rehabilitation, Chief Investigator): study conception and design, writing and reviewing of report.

Compliance with Ethical Standards

Conflict of Interest Dr Iftekhar Khan, Prof. Stavros Petrou, Mr Kamran Khan, Dr Dipesh Mistry, Dr Ranjit Lall, Dr Bart Sheehan and Prof. Sarah Lamb declare no conflicts of interest related to this study.

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Ethical Approval and Informed Consent This study was approved by the UK institutional and national research ethics committee and has been performed in accordance with the ethical standards of the Declaration of Helsinki. Informed consent was obtained from all individual participants included in the study.

Data Availability Statement The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

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