ORIGINAL RESEARCH

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Targeting Functional Decline in Alzheimer Disease

A Randomized Trial

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Background: Alzheimer disease results in progressive functional decline, leading to loss of independence.

Objective: To determine whether collaborative care plus 2 years of home-based occupational therapy delays functional decline.

Design: Randomized, controlled clinical trial. (ClinicalTrials.gov: NCT01314950)

Setting: Urban public health system.

Patients: 180 community-dwelling participants with Alzheimer disease and their informal caregivers.

Intervention: All participants received collaborative care for dementia. Patients in the intervention group also received in-home occupational therapy delivered in 24 sessions over 2 years.

Measurements: The primary outcome measure was the Alzheimer's Disease Cooperative Study Group Activities of Daily Living Scale (ADCS ADL); performance-based measures included the Short Physical Performance Battery (SPPB) and Short Portable Sarcopenia Measure (SPSM).

Results: At baseline, clinical characteristics did not differ significantly between groups; the mean Mini-Mental State Examination score for both groups was 19 (SD, 7). The intervention group received a median of 18 home visits from the study occupational therapists. In both groups, ADCS ADL scores declined over 24 months. At the primary end point of 24 months, ADCS ADL scores did not differ between groups (mean difference, 2.34 [95% CI, −5.27 to 9.96]). We also could not definitively demonstrate between-group differences in mean SPPB or SPSM values.

Limitation: The results of this trial are indeterminate and do not rule out potential clinically important effects of the intervention.

Conclusion: The authors could not definitively demonstrate whether the addition of 2 years of in-home occupational therapy to a collaborative care management model slowed the rate of functional decline among persons with Alzheimer disease. This trial underscores the burden undertaken by caregivers as they provide care for family members with Alzheimer disease and the difficulty in slowing functional decline.

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Alzheimer disease and related dementia lead to a high burden for patients, families, and society (1). Over the typical disease course of 5 to 10 years, the condition results in progressive functional disability, frequent transitions in care, and excess health care costs (2–5). Alzheimer disease has no known cure or disease-modifying treatments (6). In the context of the disease, functional decline is believed to be the result of progressive deficits in cognitive, emotional, and physical function.

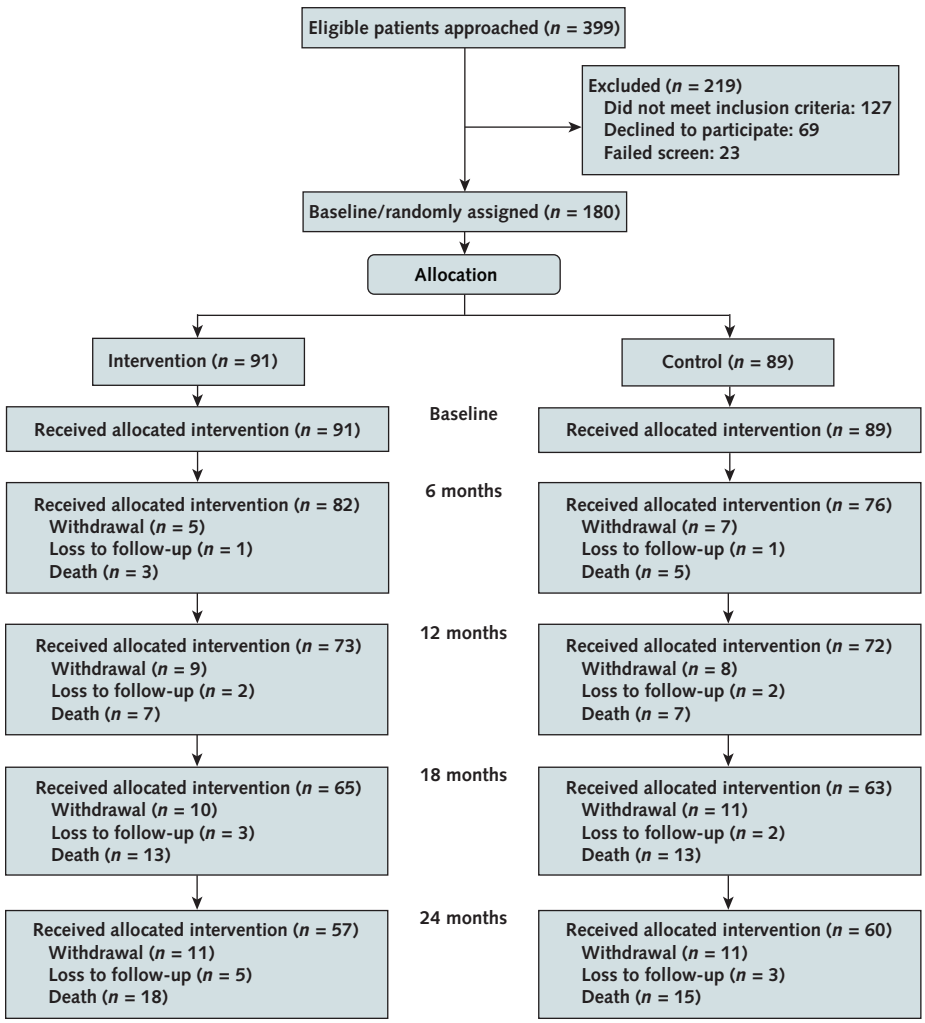
New models of Alzheimer disease care focus on a team-based approach in support of the family caregiver and seek to improve patients' quality of life (7, 8). These new care models emphasize coordination with community-based services, modifications to the patient's home, and movement toward dementia-prepared communities (9). Primary care practices often find these new models difficult to implement, because they require practice redesign, workforce retraining, community outreach, and leadership in local advocacy. Ten years ago, we reported the results of a randomized, controlled clinical trial testing the effectiveness of collaborative care among primary care patients with Alzheimer disease (10). The intervention resulted in clinically significant improvement in the quality of care and behavioral symptoms for patients and reduced stress for their family caregivers. Despite these improvements, the intervention did not slow the rate of patients' functional decline.

During the past decade, several studies focusing on functional decline among patients with Alzheimer disease have shown the potential of home-based interventions to slow this decline (11–16). The specific aim of this study was to conduct a 2-year randomized, controlled clinical trial to delay functional decline among older adults with Alzheimer disease by comparing a control group receiving best-practice primary care with an intervention group receiving best-practice primary care plus a home-based occupational therapy intervention.

Methods

The study was approved by the Indiana University–Purdue University Indianapolis Institutional Review Board. A detailed description of the study design was published previously (17). The study was a randomized, single-blind, controlled clinical trial with a parallel design and a 1:1 allocation ratio. It was conducted at Eskenazi Health, an urban public health system serving Indianapolis, Indiana. Patients were enrolled from 1 of 10 primary care practices or the 1 senior care practice affiliated with Eskenazi Health. They were eligible for participation if they were aged 45 years or older and

Figure. CONSORT diagram.



CONSORT = Consolidated Standards of Reporting Trials.

had a diagnosis of possible or probable Alzheimer disease, as determined by physicians in a memory care practice affiliated with Eskenazi Health. Eligible patients also were required to be community dwelling; to speak English; and to have a caregiver who was willing to participate in the study, had access to a telephone, and was willing to receive home visits. Research personnel assigned to each clinical site obtained written informed consent (or assent) from eligible patients and their participating family caregivers.

The CONSORT (Consolidated Standards of Reporting Trials) diagram is shown in the Figure.

Randomization was conducted at the patient level, stratified by type of clinic (primary or senior care). The lead statistician (S.G.) used the statistical software SAS (SAS Institute) to generate the randomization scheme in a block of 4. Sequentially numbered, sealed envelopes containing the randomization assignment for patients from each of the 2 clinics were prepared by the study statistician. Actual randomization results were compared with the preplanned randomization schedule, and no deviation was found.

Description of the Control Condition

Both study groups received collaborative care for dementia facilitated through the Healthy Aging Brain Center (HABC), a memory care practice that provided comanagement with the primary care practice (18, 19). We considered this approach "best-practice primary care" because it encompassed the collaborative care intervention tested in our previous clinical trial (10). Based on the patient's current symptoms, as reported by the caregiver using the HABC Monitor (20), individualized recommendations were made to manage the patient's behavioral symptoms (21). Items reported by the caregiver dictated activation of specific behavioral intervention protocols by the care manager. Each of these protocols focused first on nonpharmacologic interventions. If the nonpharmacologic approach did not result in acceptable improvement, the care manager

collaborated with the primary care or memory care practice physician to consider protocol-based drug therapy.

Description of the Intervention

The study intervention was described previously (22). Briefly, the intervention group received all of the components of best-practice primary care described earlier plus a home-based intervention designed to slow functional decline. Any study patient or caregiver, regardless of group, could receive any other concomitant care prescribed by their providers. The framework of the intervention was based on general occupational therapy principles (22) as well as interventions described in earlier published studies (11–13, 23). The main goal was to support and augment the self-care functional capability of the patient, as identified by goals established in negotiation with the patient and caregiver. The occupational therapist completed an initial in-home evaluation to develop a formal care plan tailored to the needs of the patient–caregiver dyad, and he or she repeated the evaluation at the beginning of each additional cycle. Three cycles of the home-based intervention were completed over 2 years. In the first cycle, eight 90-minute sessions were delivered approximately every other week for 16 weeks. At each visit, the therapist introduced a new task based on a mutually agreed-on care plan. In the second cycle, the 8 home visits occurred every 4 weeks and therefore were completed in 32 weeks. In the third cycle, the 8 visits took place over 1 year. Between visits, any problems or new concerns on the part of the caregiver were addressed via telephone. The phone calls continued in the same progression throughout the 3 cycles, but with more weeks between contacts. Over 2 years, each dyad could receive up to 24 homes visits by 1 or more of 5 occupational therapists or 1 occupational therapy assistant; however, only an occupational therapist, not an assistant, could complete the initial assessment and care plan.

Outcome Measures

Outcome measures were completed in each patient's home by 2 research assistants who were blinded to the dyad's randomization status. The primary outcome measure was the Alzheimer's Disease Cooperative Study Group Activities of Daily Living Scale (ADCS ADL), which assesses the traditional basic activities of daily living as well as variations in instrumental activities of daily living and several more complex and explicit self-care tasks (24). Scores vary from 0 to 75, with higher scores indicating better function. Because this scale is based on reports by the caregiver, we also completed 2 patient performance measures. The Short Physical Performance Battery (SPPB) is a standardized measure of lower-extremity physical performance that includes walking, balance, and power tasks (25–27). Scores vary from 0 to 12, with higher scores indicating better function. The Short Portable Sarcopenia Measure (SPSM), conceptualized as a measure of sarcopenia that combines muscle quantity and function (28), is based on timed chair rises, lean mass, and grip strength divided by height. Scores range from 0 to 18, with higher scores indicating better function. We previously reported good correlation between these 3 scales and caregiver-reported function across a range of patients' cognitive function (29). Those findings suggested that the patients could adequately understand and follow instructions for performing the SPPB and SPSM. To help compare our outcomes with those of our previous clinical trial of collaborative care alone, we also completed the ADCS Group Neuropsychiatric Inventory at each assessment (30–32). Scores on this instrument range from 0 to 144, with higher values representing worse symptoms. We also collected a broad range of process-of-care data.

Statistical Analysis

The study was designed for 80% power based on a 2-tailed test at a 5% significance level to test the hypothesis that patients in the intervention group would have better function than those in the control group at 24 months, with an effect size of 0.23 SD based on the ADCS ADL. Thus, the targeted sample size was 180 patients. All participants were randomly assigned according to the randomization scheme and were analyzed in the group to which they were assigned. Dementia-specific care processes were compared between the 2 groups by using 2 sample *t* or Wilcoxon rank-sum tests for continuous variables and Fisher exact tests for categorical variables. For each outcome measure collected at baseline and 6, 12, 18, and 24 months, a mixed-effects model was used, with time and an interaction between group and time as independent variables, whereas randomization stratum and within-patient correlation over time were adjusted for by using an unstructured covariance matrix. Main effect for group was not included in the mixed-effects models in order to enforce the equal group mean assumption at baseline given the randomized trial design (33).

Two sensitivity analyses were conducted to assess the potential effect of missing data (**Appendix**). First, multiple imputation for patients with missing follow-up data was done for those whose data were missing for reasons other than death. We used a regression imputation approach incorporating the patients' baseline characteristics and observed outcomes with separate group means while adjusting for randomization stratum (34). Second, we used a selection model approach to adjust for potentially nonignorable missing data. All analyses were conducted by using SAS 9.4.

Role of the Funding Source

The National Institute on Aging had no role in the design, conduct, or analysis of this study or in the decision to submit the manuscript for publication.

RESULTS

Table 1 compares the baseline characteristics of the participants. Consistent with a cohort of older adults with probable Alzheimer disease, the mean age in each group was approximately 80 years, most participants were women, and Mini-Mental State Examination

Table 1. Baseline Comparison of Characteristics of Study Participants

Characteristic	Intervention (*n* = 91)*	Usual Care (*n* = 89)†
Mean age (SD), *y*	79.6 (8.3)	77.2 (9.4)
Male, *n (%)*	25 (27)	28 (31)
Black, *n (%)*	53 (58)	49 (55)
Not a high school graduate, *n (%)*	36 (40)	44 (50)
Recruited from senior care clinic, *n (%)*	77 (85)	77 (87)
Mean body mass index (SD), kg/m^2	27.2 (5.7)	28.7 (6.4)
Mean MMSE score (SD)	19.4 (6.9)	19.0 (7.6)
Mean Word List Learning score (SD)	9.5 (5.4)	9.5 (5.9)
Mean ADCS ADL score (SD)	49.4 (17.6)	47.8 (15.7)
Mean SPSM (SD)	3.3 (3.5)	3.6 (3.7)
Mean SPPB score (SD)	4.3 (2.7)	4.2 (3.2)
Mean NPI score (SD)	15.6 (15.1)	16.6 (18.9)
Spousal caregiver, *n (%)*	20 (22)	28 (32)
Mean age of caregiver (SD), *y*	56.0 (12.3)	59.1 (12.5)
Caregiver's mean GAD-7 anxiety scale score (SD)	4.0 (4.5)	3.6 (4.5)
Caregiver's mean PHQ-9 depression scale score (SD)	4.1 (4.1)	3.7 (3.7)

ADCS ADL = Alzheimer's Disease Cooperative Study Group Activities of Daily Living Scale. GAD = Generalized Anxiety Disorder 7-item; MMSE = Mini-Mental State Examination; NPI = Neuropsychiatric Inventory; PHQ-9 = Patient Health Questionnaire-9; SPPB = Short Portable Performance Battery; SPSM = Short Portable Sarcopenia Measure.
* Sample size is <91 for education level (*n* = 90), body mass index (*n* = 80), MMSE score (*n* = 90), Word List Learning score (*n* = 90), SPSM score (*n* = 88), SPPB score (*n* = 87), and PHQ-9 score (*n* = 90).
† Sample size is <89 for education level (*n* = 88), body mass index (*n* = 78), Word List Learning score (*n* = 88), and SPSM (*n* = 86).

(MMSE) and word-list learning scores demonstrated mild to moderate cognitive impairment. Study participants also had significant impairments in activities of daily living and a high burden of behavioral problems, and their caregivers showed mild to moderate levels of anxiety and depression. Patients also had a high burden of comorbid conditions, including diabetes (30% in the intervention and 30% in the control group), depression (30% and 33%), congestive heart failure (12% and 16%), coronary artery disease (14% and 16%), and history of stroke (4% and 5%).

Table 2 summarizes the level of dementia-specific care received by the 2 study groups. Both groups received best-practice primary care for dementia through a locally adapted care management program provided by the HABC (18, 19). The dementia care the groups received approximated the collaborative care received by the participants in an earlier clinical trial (10). All study participants received their diagnosis in a memory care practice, and all were referred for care management to the home-based dementia care program. Most patients received treatment with antidementia medications. The frequency of dementia-specific care did not differ between the groups.

Table 3 describes the frequency and content of the occupational therapy intervention. Over 2 years, patients in the intervention group received a median of 18 in-home evaluations and care visits, totaling 21 hours (median) of face-to-face time with the occupational therapists. Because these visits were tailored to meet the expressed needs of each care recipient–caregiver dyad and because these needs were expected to change over time, the content of the visits varied both across and within participants over time. Table 3 shows the percentage of visits that focused on individual target areas, as reported by the occupational therapist after each visit. The focus areas are ordered by frequency in the table and demonstrate the dominance of mobility interventions, such as transfers, standing, household mobility, sitting, and home exercise, all of which were targeted in more the 50% of the home visits.

Table 4 compares the clinical outcomes between study groups. At 24 months, no statistically significant difference in ADCS ADL score was observed between the groups. Notably, the results were interpreted as indeterminate, because the 95% CI (−5.27 to 9.96) included clinically significant between-group differences (4.05, based on an effect size of 0.23). Both groups had progressive functional decline, as well as decreases in the performance-based measures of the SPPB and the SPSM, over time. According to data not shown in the table, mean MMSE scores declined in both groups over time: 19.37 to 16.76 in the intervention group and 19.02 to 17.26 in the control group. No significant difference was seen between the study groups regarding mortality over 2 years (20% vs. 17%) or in the average number of days participating in the study (577 vs. 575).

Data were missing primarily because of patient deaths; however, we completed 2 additional analyses to explore the potential effect of these data on the study outcomes. First, we used multiple imputation to account for data missing for reasons other than death. Second, we implemented the selection model ap-

Table 2. Comparison of Concomitant Dementia-Specific Care Processes Over 2 y

Care Process	Intervention (*n* = 91)	Usual Care (*n* = 89)	*P* Value
Median physician visits in HABC (IQR), *n*	2 (0–4)	2 (0–4)	0.93
Median HABC care management visits face to face in clinic or home by nurse, social worker, or care coordinator assistant (IQR), *n*	8 (4–14)	8 (4–13)	0.56
HABC care management telephone contacts by nurse, social worker, or care coordinator assistant (IQR), *n*	8 (3–17)	8 (3–13)	0.174
Receiving antidementia medication, %	62	60	0.88
Receiving antidepressant medication, %	48	54	0.46
Median nonstudy occupational therapy visits in hospital setting or outpatient facility (IQR), *n*	0 (0–1)	0 (0–1)	0.68
Median primary care practice visits (IQR), *n*	6 (2–10)	7 (2–12)	0.56
Median specialty care visits (IQR), *n*	0 (0–4)	0 (0–3)	0.95

HABC = Healthy Aging Brain Center; IQR = interquartile range.

Table 3. Frequency and Content of OT Intervention (n = 91)

Intervention	Value
Median OT home visits over 2 y (IQR), *n*	18.0 (11.0–21.0)
Median total duration of all OT home visits (IQR), *h*	20.7 (13.4–24.8)
Median average duration of each home OT visit (IQR), *min*	68.5 (64.0–73.2)
Median OT telephone contacts between visits (IQR), *n*	17 (11–22)
Mean visits by OTs targeting these priorities (95% CI), %	
Transfers	66.5 (61.2–71.8)
Household mobility	64.5 (56.7–72.3)
Standing	62.0 (56.7–72.3)
Home exercise program	56.1 (50.5–61.6)
Sitting	52.9 (46.1–59.8)
Patient or caregiver education	41.8 (33.2–50.5)
Cognition	39.6 (32.5–46.7)
Meaningful activity	36.0 (31.7–40.3)
Energy conservation	21.9 (16.7–27.0)
Safety	21.0 (15.4–26.5)
Activities of daily living	18.9 (13.9–23.9)
Toileting	16.1 (12.0–20.2)
Dressing lower	13.1 (9.8–16.3)
Dressing upper	10.3 (7.4–13.3)
Gross motor coordination	8.8 (6.0–11.7)
Feeding	8.4 (6.0–10.9)
Fine motor coordination	8.1 (5.6–10.6)
Grooming	7.4 (4.8–10.1)
Light housekeeping	7.0 (4.6–9.5)
Cooking	4.6 (2.5–6.8)
Bathing lower	3.3 (1.8–4.8)
Bathing upper	2.9 (1.5–4.3)

IQR = interquartile range; OT = occupational therapy.

proach by assuming the missing data were not ignorable and depended on unobserved outcomes. We also conducted a series of sensitivity analyses by varying the missing-data assumption. Between-group differences at 24 months remained nonsignificant in each of these analyses (**Appendix**).

DISCUSSION

The goal of this study was to determine whether a home-based occupational therapy intervention delivered over a period of 2 years could slow the rate of functional decline among older adults with Alzheimer disease. Both study groups received best-practice dementia care, which previously was demonstrated to improve behavioral outcomes and reduce caregiver stress but not to slow functional decline (10). In the earlier trial, both groups had a decrease of approximately 4 points per year on the 23-item ADCS ADL scale, which ranges from 0 to 75. On the basis of these findings and other studies in the literature, we estimated that between-group ADCS ADL differences in the range of 4 points over 2 years might be clinically significant. In the current study, we found between-group differences of 2.34 points and reported 95% CIs that include the potential for clinically significant improvement (9.96) and clinically significant decline (−5.27) in the experimental group. For this reason, the results of this trial should be considered indeterminate (35). Patients with Alzheimer disease and several chronic conditions have a high mortality rate (2); nearly 1 in 5 participants died during the 2-year follow-up. However, the findings remained consistent across a range of analytic approaches to missing data.

On the basis of previous, shorter-term studies of related interventions (11–14), we hypothesized that this intervention might slow the rate of functional decline through 3 potential mechanisms. First, the social, physical, and cognitive approach encompassed by occupational therapy might actually slow the pathologic processes of Alzheimer disease or stimulate compensatory cognitive mechanisms. Second, the intervention might have no effect on Alzheimer disease pathology but instead might improve functional decline emanating from other diseases and conditions comorbid with the dementing illness, including frailty from consequential behaviors, such as inactivity, boredom, or social withdrawal. Third, the occupational therapy might have no effect on any disease or results of sedentary behavior among the patients, but it might improve the caregiver's perception of functional decline through caregiver training in such areas as transfers and toileting. Because caregiver-reported patient function, as well as performance-based and cognitive function measures, continued to decline over time in both study groups, we cannot provide support for these posited mechanisms of action for occupational therapy.

The trial had 4 important strengths beyond the randomized, controlled study design. First, we could compare the effect of the intervention over and above that of best-practice dementia care. This aspect of the trial is fundamental to the examination of the unique contribution of longer-term occupational therapy. Second, we included a broad range of outcome measures that involved not only caregiver-reported patient function and performance-based measures of function but also measures of cognition, mood, and behavioral symptoms. Third, we could document the process of care, including the content and duration of the occupational therapy intervention, the content of concomitant dementia-specific care, and the content of the concomitant primary and specialty care received by the study participants. Fourth, we believe that this was the first trial of occupational therapy among persons with probable Alzheimer disease that followed participants for 2 years.

Previous research exploring the capacity to slow functional decline in older adults with Alzheimer disease by using different interventions produced mixed results (16, 36–39). In 2013, Pitkälä and colleagues (40) reported a home-based exercise study among persons with Alzheimer disease in Finland and compared this intervention with group-based exercise and with usual care. As in the current study, the authors found that function among all 3 groups declined over time and that SPPB scores did not differ significantly between the groups at 12 months. However, unlike our study, Pitkälä and coworkers' research revealed that functional decline among members of the home-based exercise group was significantly less at 12 months, as determined by the caregiver-reported Functional Independence Measure. The author of an accompanying edito-

Table 4. Mixed-Effects Model Results for Outcome Measures at 6, 12, 18, and 24 mo*

Visit	Predicted Mean (95% CI)		Between-Group Difference (95% CI)	*P* Value
	Intervention	Usual Care		
ADCS ADL score				
6 mo	45.49 (41.02 to 49.96)	43.57 (38.97 to 48.18)	1.92 (−3.49 to 7.32)	0.49
12 mo	43.25 (38.33 to 48.17)	39.36 (34.33 to 44.39)	3.89 (−2.24 to 10.01)	0.21
18 mo	39.10 (33.96 to 44.24)	36.32 (31.06 to 41.58)	2.78 (−3.71 to 9.27)	0.40
24 mo	34.47 (28.60 to 40.34)	32.13 (26.17 to 38.08)	2.34 (−5.27 to 9.96)	0.54
SPPB total score				
6 mo	3.88 (3.08 to 4.68)	4.08 (3.25 to 4.91)	−0.20 (−1.19 to 0.78)	0.68
12 mo	3.88 (3.04 to 4.72)	3.75 (2.88 to 4.61)	0.14 (−0.91 to 1.18)	0.80
18 mo	3.52 (2.65 to 4.38)	3.16 (2.26 to 4.05)	0.36 (−0.72 to 1.45)	0.51
24 mo	2.45 (1.55 to 3.35)	2.78 (1.87 to 3.69)	−0.33 (−1.46 to 0.80)	0.57
SPSM total score				
6 mo	1.85 (1.00 to 2.70)	2.87 (1.98 to 3.76)	−1.02 (−2.05 to 0.02)	0.05
12 mo	2.00 (1.13 to 2.87)	2.26 (1.35 to 3.16)	−0.25 (−1.32 to 0.82)	0.64
18 mo	1.63 (0.72 to 2.53)	2.06 (1.11 to 3.00)	−0.43 (−1.56 to 0.70)	0.45
24 mo	1.48 (0.56 to 2.41)	2.11 (1.15 to 3.07)	−0.62 (−1.78 to 0.53)	0.29
NPI frequency score × severity score				
6 mo	13.51 (9.44 to 17.57)	17.80 (13.58 to 22.02)	−4.29 (−9.31 to 0.73)	0.09
12 mo	13.99 (9.66 to 18.31)	18.29 (13.88 to 22.71)	−4.31 (−9.71 to 1.09)	0.12
18 mo	14.96 (10.75 to 19.17)	15.66 (11.30 to 20.02)	−0.71 (−5.96 to 4.55)	0.79
24 mo	14.68 (9.97 to 19.38)	19.13 (14.35 to 23.90)	−4.45 (−10.4 to 1.54)	0.14
PHQ-9 total score				
6 mo	3.48 (2.56 to 4.40)	4.07 (3.11 to 5.03)	−0.59 (−1.73 to 0.56)	0.31
12 mo	3.65 (2.68 to 4.61)	4.79 (3.80 to 5.78)	−1.14 (−2.34 to 0.06)	0.06
18 mo	3.80 (2.81 to 4.79)	3.83 (2.80 to 4.85)	−0.03 (−1.28 to 1.23)	0.97
24 mo	3.72 (2.78 to 4.67)	3.70 (2.73 to 4.67)	0.02 (−1.15 to 1.20)	0.97
GAD-7 scale total score				
6 mo	3.22 (2.19 to 4.24)	3.37 (2.30 to 4.43)	−0.15 (−1.42 to 1.12)	0.82
12 mo	3.21 (2.14 to 4.28)	4.16 (3.07 to 5.26)	−0.95 (−2.29 to 0.39)	0.16
18 mo	3.46 (2.48 to 4.44)	2.75 (1.73 to 3.77)	0.71 (−0.49 to 1.92)	0.25
24 mo	2.86 (1.87 to 3.85)	2.84 (1.83 to 3.86)	0.01 (−1.20 to 1.23)	0.98

ADCS ADL = Alzheimer's Disease Cooperative Study Group Activities of Daily Living Scale; GAD-7 = Generalized Anxiety Disorder 7-item; NPI = Neuropsychiatric Inventory; PHQ-9 = Patient Health Questionnaire-9; SPPB = Short Portable Performance Battery; SPSM = Short Portable Sarcopenia Measure.
* Results include predicted means and 95% CIs from mixed-effects models adjusting for randomization strata accounting for repeated assessments over time within the participant.

rial questioned the limited clinical significance of this difference (41). The present study enrolled older adults with ages and baseline MMSE scores similar to those of the Finnish study participants, but Pitkälä and colleagues enrolled volunteers who could walk independently at baseline (with or without a walking aid) and had a spousal caregiver. Participants in the current study were not excluded on the basis of those 2 criteria and were enrolled from clinical populations; they had significantly lower SPPB scores at baseline, were less likely to have a spousal caregiver, had more comorbid conditions, and were followed for 2 years. In 2016, Toots and colleagues (42) reported a randomized trial of intensive exercise among older adults with Alzheimer disease enrolled from residential care facilities in Sweden. The intervention included a functional exercise program that focused on lower-limb strength and balance. This study also showed no evidence of a delayed decline in activities of daily living at 7 months.

Our study has limitations. A longer observation period, a more intensive occupational therapy intervention, the enrollment of older adults earlier in the course of their dementing illness or with lower levels of multimorbidity, or a larger sample size receiving the identical intervention may have produced more encouraging results. Several reasons have been posited for why the intervention was less effective than anticipated. First, participants may have been unable to learn the recommended tasks and activities promoted by the occupational therapy interventions. Second, caregivers enrolled in this study may have been less able or less motivated than other caregivers to adhere to the protocol. Third, dyads may have had health priorities with regard to functional decline that were not captured by the ADCS ADL scale. Fourth, occupational therapy may be necessary but insufficient to slow the rate of functional decline; if our intervention combined occupational therapy with other potential interventions, we may have obtained different results. We stress that this trial was not a test of the potential benefits of occupational therapy for acute conditions among older adults with dementia, nor a test of the benefits of collaborative care for older adults with dementia.

Long-term home-based occupational therapy is not the current standard of care for older adults with Alzheimer disease, although many experts recommend strategies that promote continued physical, social, and cognitive activity. Medicare Part B and Medicaid provide coverage for outpatient rehabilitation therapy if it meets the criteria for being "medically necessary and reasonable." For most Medicare beneficiaries, this benefit is capped at approximately $2000 per year, with most beneficiaries responsible for a 20% copayment, although providers may request additional therapy on the basis of medical necessity. In the present trial, patients were not charged for occupational therapy; however, we estimated the cost of this intervention to be about $2100 per year. Our original hypothesis presumed that the benefit of occupational therapy in the targeted patient population was unproven. Although the definition of *medically necessary and reasonable* would be expected to vary among patients and health insurance plans, it often stipulates that the therapy require an occupational therapist's expertise and have a reasonable potential to provide benefit. For rehabilitation services, this benefit often requires that the patient show evidence of improvement or maintenance of function based on the provided therapy. From both clinical and policy perspectives, the present study does not provide clear evidence to support a change in current clinical practice or policy coverage.

Our findings suggest that persons with dementia face a steady decline in function that is not slowed by collaborative care and may continue even with home-based occupational therapy. We report indeterminate results regarding the question of whether occupational therapy slows the rate of functional decline relative to collaborative care alone. Given the burden of caring for persons with dementia, which largely is shouldered by family members, research must focus on identifying strategies to support caregivers in the home to provide care to persons with dementia. If the gradual functional decline attributable to Alzheimer disease is irreversible, a new generation of assistive devices, home modifications, community services, and technologies is needed to make longer-term support in the home a practical reality for patients and families.

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Reproducible Research Statement: *Study protocol:* See earlier study by Callahan and colleagues (17). *Statistical code and data set:* Available from Dr. Callahan (e-mail, ccallaha@iu.edu).

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Appendix: Supplemental Statistical Analyses

In the Appendix Figure, we present mean ADCS ADL scores over time in both the intervention and usual-care groups by the number of completed evaluations. Sample sizes for each group are noted at the end of each line plot. Patients who completed all evaluations had better ADCS ADL scores overall than those who did not complete the follow-up. Although participants who completed only 2 or 3 evaluations showed a trend toward greater decline in ADCS ADL scores, these data do not seem to suggest consistent differential declines between the 2 groups.

Two approaches were used to adjust for missing data: a multiple imputation strategy that assumed the data were missing at random (MAR) and a selection model approach that assumed the missing data were nonignorable. Here, we describe each approach in detail.

Multiple Imputation

Imputations were conducted in 2 stages. In the first stage, we dealt with intermittent missing data (an evaluation was missing but another occurred at a later follow-up time) on ADCS ADL scores from 8 patients by using imputation based on previous evaluations in the order in which they occurred. In the second stage, we used linear regression models to impute missing outcomes based on the outcomes observed from a previous evaluation by using the predictive mean matching method and allowing separate group means while adjusting for randomization stratum. In this approach, we did not impute outcomes for a patient after he or she died; these values were left as missing.

For each imputed data set, we used mixed-effects models using repeated measures from baseline and 6, 12, 18, and 24 months, with time and an interaction between group and time as independent variables, while adjusting for randomization stratum and within-patient correlation over time by using an unstructured covariance matrix. Post hoc comparisons between groups at 12 and 24 months are presented in Appendix Table 1.

Nonignorable Missing Data Adjustment

The multiple imputation approach assumes that the probability of missing data depends on observed data (MAR). A nonignorable missing-data adjustment extends the MAR assumption to allow that the missing data mechanism depends on the missing observations. A selection model approach uses the joint modeling of an outcome model and the missing mechanism with the advantage of clear interpretation of model parameters of the outcome model (43). The adoption of a selection model approach allows us to compare results with those obtained from the mixed-effects model and multiple imputations.

We assume the following longitudinal model for an outcome variable:

$$y_{ij} = \mu_0 + \mu_{kj} * I(treatment = k) + \beta * stratum + \gamma_i + \epsilon_{ij},$$

where i is the subject index; j is the index for the number of evaluations; $j = 0, 1, \ldots, 4$, k is the treatment group indicator, $k = 1$ for the intervention group and $k = 2$ for the usual-care group; γ_i is a random subject effect; and ϵ_{ij} is the random measurement error associated with each outcome measure. Notice that in this model, group difference at baseline (time 0) is assumed equal via the use of a common parameter, μ_0, because of the randomized, controlled design of the trial.

Let r_{ij} be a missing-data indicator:

$$r_{ij} = \begin{cases} 0 & \text{if } y_{ij} \text{ is observed} \\ 1 & \text{if } y_{ij} \text{ is missing} \end{cases}$$

Let $p_{ij} = Prob(r_{ij} = 1)$. We assume a logistic model for the probability of missing outcomes; that is,

$$\log \frac{p_{ij}}{1-p_{ij}} = a_1 * age + a_2 * male + \varphi_{k1} * I_k$$

$$+ \varphi_{k2} * I_k * y_{i(j-1)} + \varphi_{k3} * I_k * y_{ij},$$

where I_k is the indicator variable for treatment groups.

The joint likelihood function using a selection model approach may be written as

$$f(y_{ij}, r_{ij} \mid \mu, \beta, a, \Psi) = f(y_{ij} \mid \mu, \beta)\, f(r_{ij} \mid y, a, \Psi)$$

Estimation for the selection model approach requires integration over both the random subject effects and the missing data. A maximum likelihood estimation may be carried out by using the expectation–maximization algorithm. However, such an approach is not readily available in the SAS system. Alternatively, a Bayesian approach may be used, treating the missing data as unknown parameters, and carried out in Markov chain Monte Carlo (MCMC) simulations. Because an MCMC procedure is available in SAS, we adopted this procedure to fit the models defined earlier.

For each outcome, we generated 50 000 MCMC samples and estimated the model parameters by using the models described earlier. We assumed noninformative priors for all fixed-effect parameters. We further assumed that the subject random effect, γ_i, follows a normal distribution and the variance–covariance matrix for ε_{ij} follows an inverse-Wishart distribution.

In **Appendix Table 1**, we report results from the selection model estimation. Group means at 12 and 24 months are estimated by $\hat{\mu}_0 + \hat{\mu}_{k2} + \hat{\beta}$* *mean (stratum)* and $\hat{\mu}_0 + \hat{\mu}_{k4} + \hat{\beta}$* *mean (stratum)*, respectively. Between-group differences at 12 and 24 months are estimated by $\hat{\mu}_{12} - \hat{\mu}_{22}$ and $\hat{\mu}_{14} - \hat{\mu}_{24}$, respectively. The values in the "*P* Value" column are the posterior probability favoring no intervention effect (null hypothesis).

Parameter estimates for the dependency on the outcome at a preceding evaluation ($\phi_{12} = -0.0841$ and $\phi_{22} = -0.0013$) were negative for both groups, although not significantly, suggesting that participants with higher function in activities of daily living were less likely to have missing data at the next evaluation. It is worth noting that parameter estimates in the missing-data model for the current outcome values ($\phi_{13} = 0.0469$ and $\phi_{23} = -0.0104$) were not significantly different from 0 in either group, suggesting that no strong evidence exists for the nonignorable missing assumption under our model setup. Of course, this does not rule out a potential dependency of missing data on unobserved values under alternative model assumptions.

We conducted sensitivity analyses assuming a varying degree of missing-data dependency on the missing observations. In **Appendix Table 2**, we report results on the main outcome of ADCS ADL scores at 24 months for these scenarios. The scenarios included various situations with differential missing-data probabilities between the 2 groups by assuming that higher ADCS ADL scores are related to higher or lower missing-data probabilities. Model 1 is an MAR model assuming that the probability of missing data depends on the outcome collected 6 months prior. Models 2 and 5 assume that higher ADCS ADL scores are associated with greater missing-data probability, whereas models 3, 4, 6, and 7 assume that higher scores are associated with lower missing-data probability. We also include results from our use of the estimated selection model parameters based on the data. For comparison purposes, we also include results from the mixed-effect model and the multiple imputation. The CIs for between-group differences at 24 months from all scenarios indicate no significant intervention effect.

Web-Only Reference

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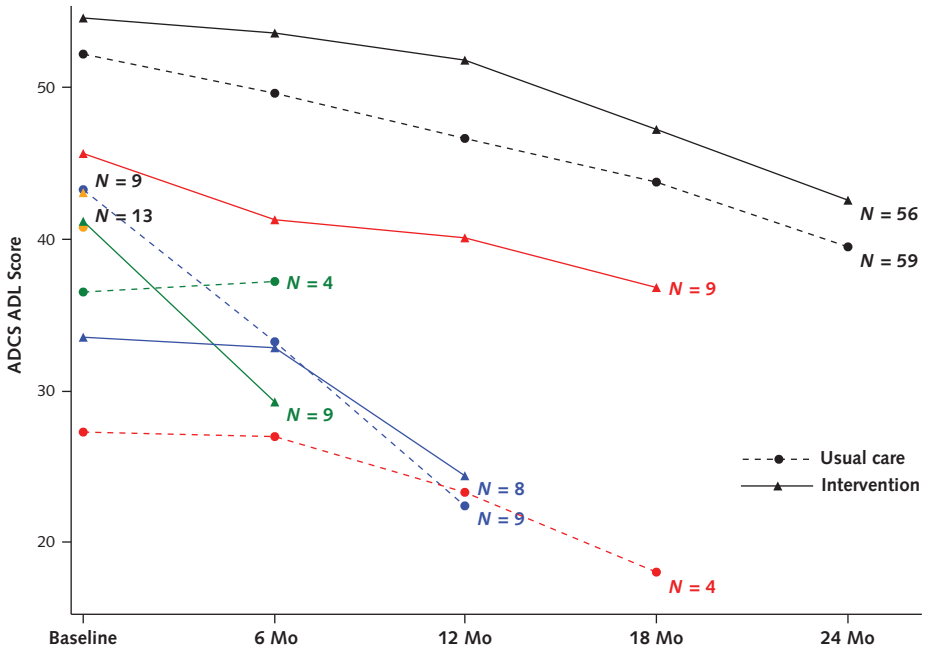
Appendix Figure. Mean ADCS ADL scores over time by the number of completed evaluations.



ADCS ADL = Alzheimer's Disease Cooperative Study Group Activities of Daily Living Scale.

Appendix Table 1. Comparison of Clinical Outcomes Adjusting for Missing Outcomes Using Multiple Imputation and Selection Model Approaches

Visit	Predicted Mean (95% CI)		Between-Group Difference (95% CI)*	*P* Value*
	Intervention	Usual Care		
Multiple imputation				
ADCS ADL score				
12 mo	40.34 (35.53 to 45.15)	43.53 (38.82 to 48.24)	3.19 (−2.62 to 9.00)	0.2819
24 mo	34.31 (29.12 to 39.50)	37.20 (32.11 to 42.28)	2.88 (−3.57 to 9.33)	0.3808
SPPB total score				
12 mo	3.77 (2.96 to 4.58)	3.98 (3.20 to 4.77)	0.21 (−0.75 to 1.18)	0.6671
24 mo	2.98 (2.17 to 3.80)	2.83 (2.04 to 3.62)	−0.15 (−1.15 to 0.84)	0.7622
SPSM total score				
12 mo	2.37 (1.50 to 3.23)	2.13 (1.31 to 2.95)	−0.23 (−1.23 to 0.76)	0.6446
24 mo	2.12 (1.22 to 3.01)	1.48 (0.63 to 2.33)	−0.64 (−1.69 to 0.41)	0.2317
NPI total score				
12 mo	17.44 (12.84 to 22.05)	15.24 (10.74 to 19.73)	−2.20 (−7.83 to 3.42)	0.4421
24 mo	17.84 (13.18 to 22.50)	15.79 (11.18 to 20.39)	−2.05 (−7.78 to 3.67)	0.4820
PHQ-9 total score				
12 mo	4.71 (3.72 to 5.69)	3.78 (2.81 to 4.76)	−0.92 (−2.09 to 0.25)	0.1229
24 mo	3.91 (2.94 to 4.88)	3.76 (2.81 to 4.72)	−0.15 (−1.31 to 1.02)	0.8066
GAD-7 scale total score				
12 mo	4.06 (2.97 to 5.16)	3.36 (2.31 to 4.42)	−0.70 (−2.03 to 0.62)	0.2992
24 mo	3.08 (2.05 to 4.11)	3.08 (2.05 to 4.12)	0.00 (−1.25 to 1.26)	0.9949
Nonignorable missing data model				**Posterior *P* Value†**
ADCS ADL score				
12 mo	43.58 (40.02 to 47.03)	41.25 (37.76 to 44.90)	2.34 (−1.24 to 5.91)	0.0994
24 mo	34.70 (29.76 to 39.36)	33.93 (28.87 to 38.88)	0.77 (−5.24 to 6.68)	0.3967
SPPB total score				
12 mo	3.98 (3.38 to 4.59)	3.92 (3.27 to 4.55)	0.07 (−0.64 to 0.78)	0.4243
24 mo	2.65 (1.91 to 3.38)	3.00 (2.24 to 3.70)	−0.36 (−1.25 to 0.53)	0.7874
SPSM total score				
12 mo	2.66 (2.02 to 3.29)	2.69 (2.04 to 3.32)	−0.03 (−0.80 to 0.74)	0.5309
24 mo	2.17 (1.48 to 2.90)	2.58 (1.86 to 3.32)	−0.41 (−1.34 to 0.53)	0.8118
NPI total score				
12 mo	13.82 (10.25 to 17.16)	17.73 (14.22 to 21.21)	−3.86 (−8.12 to 0.50)	0.0441
24 mo	14.88 (10.97 to 18.88)	18.66 (14.81 to 22.54)	−3.78 (−8.68 to 1.16)	0.0664
PHQ-9 total score				
12 mo	3.71 (2.92 to 4.49)	4.99 (4.18 to 5.79)	−1.25 (−2.29 to −0.20)	0.0096
24 mo	3.65 (2.90 to 4.43)	3.87 (3.12 to 4.62)	−0.25 (−1.28 to 0.72)	0.3141
GAD-7 scale total score				
12 mo	3.20 (2.38 to 4.03)	4.43 (3.59 to 5.29)	−1.23 (−2.24 to −0.19)	0.0123
24 mo	2.87 (2.11 to 3.66)	3.11 (2.34 to 3.87)	−0.24 (−1.17 to 0.72)	0.3116

ADCS ADL = Alzheimer's Disease Cooperative Study Group Activities of Daily Living Scale; GAD-7 = Generalized Anxiety Disorder 7-item; NPI = Neuropsychiatric Inventory; PHQ-9 = Patient Health Questionnaire-9; SPPB = Short Portable Performance Battery; SPSM = Short Portable Sarcopenia Measure.

* For multiple imputation, outcomes are compared using mixed-effects models adjusting for randomization stratum and within-patient correlations using multiple imputed data sets.

† Posterior probabilities of estimated between-group difference favor the usual care group (the null hypothesis).

Appendix Table 2. Sensitivity Analyses for Between-Group Differences in the Alzheimer's Disease Cooperative Study Group Activities of Daily Living Inventory Score at 24 mo

Variable	Predicted Mean (95% CI)		Between-Group Difference (95% CI)	*P* Value
	Intervention	Usual Care		
Mixed-effects model	34.47 (28.60 to 40.34)	32.13 (26.17 to 38.08)	2.34 (−5.27 to 9.96)	0.5446
Multiple imputation	34.31 (29.12 to 39.50)	37.20 (32.11 to 42.28)	2.88 (−3.57 to 9.33)	0.3808
Nonignorable missing models	34.70 (29.76 to 39.36)	33.93 (28.87 to 38.88)	0.77 (−5.24 to 6.68)	0.3967
Sensitivity analyses†				**Posterior *P* Value***
1. $\phi_{13} = 0$, $\phi_{23} = 0$	34.88 (29.97 to 39.97)	34.02 (29.14 to 38.95)	0.86 (−4.84 to 6.70)	0.3898
2. $\phi_{13} = 0$, $\phi_{23} = 0.2$	34.86 (29.85 to 39.90)	33.98 (29.16 to 38.69)	0.88 (−5.17 to 6.79)	0.3749
3. $\phi_{13} = 0$, $\phi_{23} = -0.2$	34.80 (29.83 to 39.62)	34.11 (29.17 to 38.87)	0.69 (−5.22 to 6.39)	0.4051
4. $\phi_{13} = 0$, $\phi_{23} = -0.4$	34.73 (29.87 to 39.56)	34.06 (29.21 to 38.84)	0.67 (−5.18 to 6.33)	0.4106
5. $\phi_{13} = 0.2$, $\phi_{23} = 0$	34.59 (29.52 to 39.53)	34.03 (29.17 to 38.78)	0.56 (−5.44 to 6.47)	0.4258
6. $\phi_{13} = -0.2$, $\phi_{23} = 0$	35.02 (30.10 to 39.90)	34.13 (29.27 to 39.07)	0.89 (−4.96 to 6.92)	0.3830
7. $\phi_{13} = -0.4$, $\phi_{23} = 0$	34.85 (27.81 to 40.52)	32.92 (24.02 to 38.20)	1.94 (−4.16 to 8.79)	0.2951

* Posterior probabilities of the estimated between-group difference favor the usual care group (the null hypothesis).
† Sensitivity analyses based on alternate nonignorable missing data assumptions: $\phi_{13} = 0$, in the intervention group, missing data probability does not depend on the missing outcome; $\phi_{13} > 0$, in the intervention group, higher Alzheimer's Disease Cooperative Study Group Activities of Daily Living Inventory scores are associated with higher missing data probability; $\phi_{13} < 0$, in the intervention group, higher scores are associated with lower missing data probability; $\phi_{23} = 0$, in the usual care group, missing data probability does not depend on the missing outcome; $\phi_{23} > 0$, in the usual care group, higher scores are associated with higher missing data probability; and $\phi_{23} < 0$, in the usual care group, higher scores are associated with lower missing data probability.