



Three-year follow-up on the efficacy of psychosocial interventions for patients with mild dementia and their caregivers: the multicentre, rater blinded, randomized Danish Alzheimer Intervention Study (DAISY)

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4 **Three-year follow-up on the efficacy of psychosocial interventions for patients with mild**
5 **dementia and their caregivers: the multicentre, rater blinded, randomised Danish Alzheimer**
6 **Intervention Study (DAISY)**
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29 [trials.com/ISRCTN74848736](http://www.controlled-trials.com/ISRCTN74848736)).
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Abstract

Objectives: To examine the long-term efficacy at 36-month follow-up of an early psychosocial counselling and support programme lasting 8-12 months for community-dwelling patients with mild Alzheimer's disease and their caregivers.

Design: Multicentre, randomised, controlled, rater-blinded trial.

Setting: Primary care and memory clinics in five Danish districts.

Participants: 330 home-dwelling patients with mild Alzheimer's disease and their primary caregivers (dyads).

Interventions: Dyads were randomized to receive intervention during the first year after diagnosis and follow-up at 3, 6, 12, and 36 months in the intervention group or follow-up only in the control group.

Main outcome measures: Primary outcomes for the patients assessed at 36-month follow-up were changes from baseline in global cognitive function (Mini Mental State Examination), depressive symptoms (Cornell Depression Scale), and proxy rated EuroQoL quality of life on visual analogue scale. The primary outcomes for the caregivers were changes from baseline in depressive symptoms (Geriatric Depression Scale) and self-rated EuroQoL quality of life on visual analogue scale. The secondary outcome measures for the patient were proxy rated Quality of Life Scale for Alzheimer's Disease (QoL-AD), Neuropsychiatric Inventory-Questionnaire, Alzheimer's Disease Cooperative Study Activities of Daily Living Scale, all-cause mortality, and nursing home placement.

Results: At 36-month follow-up, two years after the completion of the DAISY intervention, the positive trends previously detected at 12-month follow-up in one patient primary outcome (Cornell depression score) and one patient secondary outcome (proxy-rated QoL-AD) disappeared (Cornell depression score, $P = 0.93$; proxy-rated QoL-AD, $P = 0.81$). No long-term effect of DAISY intervention on any other primary and secondary outcomes at 36-month follow-up was found.

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4 Conclusions: For patients with very mild dementia and low level of distress, initial need assessment
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6 is of paramount importance to determine whether intervention is necessary and to tailor the
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8 intervention modalities accordingly. Regular reassessments are needed to modify the interventions
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10 longitudinally.
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12 **Article summary**

13 Article focus:

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17 • Psychosocial intervention for caregivers of patients with Alzheimer's disease has been
18 shown to have beneficial effects on patients' and caregivers' psychological morbidity.
19
20 Results are inconsistent concerning nursing home placement of the patients. Studies with
21
22 psychosocial intervention for both patients and caregivers are scarce. Few have targeted
23
24 patients with very mild Alzheimer's disease. In general, there is a lack of long-term follow
25
26 up beyond 12 months.
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- 29 • It was hypothesized that the DAISY (Danish Alzheimer Intervention Study) interventions, a
30
31 multifaceted and semi-tailored intervention programme offered to patients with AD and
32
33 their primary caregivers during the first year after the diagnosis, could have a long-term
34
35 effect in preventing the emergence of depressive symptoms, improving quality of life for the
36
37 patients and the caregivers, stabilising the patients' cognitive function, and delaying nursing
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39 home placement
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45 Key messages

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47 • An intensive, multicomponent, semi-tailored psychosocial intervention program with
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49 counselling, education, and support to patients with very mild Alzheimer's disease and their
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51 caregivers during the first year after diagnosis did not improve the three-year outcomes
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53 concerning patients' and caregivers' psychological morbidity and patients' nursing home
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55 placement compared to structured and systematic follow-up support.
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- To maximize benefit, economize resources, and avoid unnecessary intervention burden, the needs of patients with very mild dementia their caregivers should be assessed to determine whether psychosocial intervention is necessary and tailor the intervention modalities accordingly. Regular reassessments are needed to identify emerging needs and modify the interventions longitudinally.

Strengths and limitations

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- This is the largest randomised controlled trial of early psychosocial intervention for patients with mild Alzheimer' disease and their caregivers to date, with a long follow-up of three years.
 - It is a study of solid methodology, strictly adhering to CONSORT recommendations.
 - The multicomponent semi-tailored intervention programme was intensive in both content and duration, targeted multiple needs, tended to the individual needs, and simultaneously involved caregivers and patients; thus having the characteristics that defined successful intervention programs documented in the literature.
 - Multiple primary and secondary outcomes were chosen based on the specific aims of the DAISY intervention and on the outcomes from similar intervention studies for patients with more advanced dementia. To avoid finding spurious effects, a conservative significance level was set at $P = 0.0005$.
 - All patients had primary caregivers who are very involved in caregiving, a situation that cannot be generalised to all patients with dementia in Denmark.
 - There was no need assessment at baseline.
 - Intervention lasted one year but without continuous follow-up and support during the subsequent two years.

INTRODUCTION

Psychosocial interventions for patients with Alzheimer's disease (AD) and their caregivers have gained recognition during the last two decades. The majority of patients with dementia live in their own homes with their caregivers, usually their spouses, who bear the responsibility of caregiving.¹ Caring for family members with dementia has long been considered as the most stressful type of family caregiving, predisposing caregivers to mental and physical illnesses and increasing their risk for death.² Previously an under-researched area, the needs of patients with AD have received more attention in recent years, with studies documenting their needs for information about their illness, for help to cope with their disabilities, for social recognition and support, and for a decent quality of life with meaningful social contact and activities.³ Patients' unmet needs can result in mood and behavioural problems, safety issues, social isolation, and increased risk for nursing home placement and death.⁴ Meta-analyses and systematic reviews of the numerous clinical trials assessing the efficacy of psychosocial interventions for caregivers have shown a significant effect of interventions on reducing caregivers' psychological morbidity and reduce patients' neuropsychiatric symptoms.^{5,6,7,8,9} Studies examining the effect of psychosocial intervention on patients' mortality and nursing home placement are scarce and the results are inconsistent.^{5,10} Studies that included psychosocial interventions for the patients are limited, providing anecdotal evidence for positive effects of interventions on patients' cognitive function, psychological morbidity, and time to nursing home placement.¹⁰ Today, thanks to the remarkable advances in diagnosing dementia, patients can be diagnosed at an early stage when their relatively intact autonomy and insight enable them to convey their needs and actively participate in intervention programmes. The rapidly growing number of people with AD in the coming years, a considerable proportion of them diagnosed in the early stages, presents a pressing need to develop

and validate intervention programmes that focus on the needs of patients with mild dementia and their caregiver and involve both parties in the intervention.

It was hypothesized that the DAISY (Danish Alzheimer Intervention Study) interventions, a multifaceted and semi-tailored intervention programme offered to patients with AD and their primary caregivers during the first year after the diagnosis, could have a long-term effect in preventing the emergence of depressive symptoms, improving quality of life for the patients and the caregivers, stabilising the patients' cognitive function, and delaying nursing home placement.¹ The results of the 12-month follow-up were published in BMJ in 2012, showing no significant difference in outcomes between the DAISY intervention and the control groups.¹¹ However, the significant level corrected for multiple testing ($P=0.0005$) was subsequently criticized for being too conservative, given that an alternative correction method could have given another conclusion.¹² At 12-month follow-up, there were indeed positive trends in one primary patient outcome (Cornell depression Scale score, $P = 0.0103$) and one secondary patient outcome (proxy-rated quality of life QoL-AD, $P = 0.0013$) in favour of the DAISY intervention group.¹¹ Therefore, a 36-month follow-up was subsequently carried out to follow the evolution of these positive trends. This paper reports on the results of this follow-up.

METHODS

Detailed description of the study rationale, methods, design, randomisation, and sample size has been published.¹

Trial Design

DAISY was a large multicentre, rater blinded, one-year randomised controlled trial of the efficacy of intensive psychosocial intervention for patients with mild AD and their caregivers. It was an exploratory randomised clinical trial with multiple primary and secondary outcomes.

Participants

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4 The patients were recruited from five Danish districts. One designated memory clinic
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6 in each district recruited the patients for the trial. Each recruiting centre had one study coordinator
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8 and one physician who assessed the patients for eligibility. Patients were referred from local
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10 memory clinics as well as private practice in psychiatry, neurology, geriatrics and family medicine.
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12 If referred from private practice, dementia diagnosis was confirmed by specialists in the recruiting
13
14 memory clinic.
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17 The inclusion criteria were: 1) Home living patients diagnosed within the past 12
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19 months with AD, mixed AD with vascular component, or Lewy body dementia, 2) 50 years of age
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21 or older, 3) Mini Mental State Examination (MMSE) score ≥ 20 ,¹³ and 4) having one participating
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23 primary caregiver. The primary caregiver was defined as the main person responsible for the
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25 informal care of the patient with minimum weekly contact. All patients met DSM-IV criteria for
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27 dementia,¹⁴ NINCDS-ADRDA criteria for probable Alzheimer's disease,¹⁵ or McKeith criteria for
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29 Lewy Body dementia.¹⁶ Patients with mixed Alzheimer's disease were those with probable
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31 Alzheimer's disease and minor vascular changes on cranial CT that could contribute to their
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33 symptoms.
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37 Patients with severe somatic or psychiatric co-morbidities (including impaired hearing
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39 or vision) that would significantly impair their compliance with the DAISY intervention programme
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41 were excluded. Patients who had already been involved in other intervention programmes were also
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43 excluded. Patient-caregiver dyads were randomised to the DAISY intervention group, in which they
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45 were provided with intensive psychosocial interventions and follow-up support at 3, 6, and 12
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47 months; or to the control group, in which they were only provided with follow-up support at 3, 6,
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49 and 12 months. The study was subsequently extended and the patients and their caregivers were
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51 asked to give a separate consent to an additional follow-up at 36 months.
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54 55 *Intervention* 56 57 58 59 60

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4 A multifaceted and semi-tailored psychosocial intervention programme, described in
5 details in our previous reports,^{1,11} was designed to provide counselling, information, and support to
6 patients with mild dementia and their caregivers in the intervention group. The study coordinator in
7 each centre, an experienced nurse specialising in caring for patients with dementia and having
8 received special training in counselling for the study (constructivist approach),¹⁷ implemented the
9 intervention within the first month after inclusion in the trial. Consisting of five key components,
10 the intervention focused on positive resources, intact function, retained skills, and feasible activities
11 for the patients: 1) The study coordinator provided seven individual counselling sessions tailored to
12 the needs of the patients and their caregivers: two for the patient alone, two for the caregiver alone,
13 two for the patient-caregiver dyad, and one with the dyad together with their family network
14 (optional); 2) The study coordinator provided outreach telephone counselling 5-8 times with 3-4
15 week intervals to maintain regular contact and follow up on the individual counselling sessions; 3)
16 Using log books, the patients and their caregivers independently kept track of the thoughts and daily
17 issues that they wanted to discuss at the counselling sessions; 4) Experts in the field of dementia
18 were invited to teach five standard courses as group intervention with separate courses for patients
19 and caregivers to provide general information about dementia and forum for discussion, sharing
20 information, and support; 5) Patients and caregivers were provided with information folders
21 produced especially for the purpose of the study about dementia causes, diagnosis and treatment,
22 legal issues, and resources for social support. The intervention program lasted 8 to 12 months. Full
23 compliance was defined as adherence with the major components of the intervention program:
24 Patients who participated with their caregivers in at least 3 counselling sessions (not including the
25 optional network session) and in at least 3 teaching course sessions.
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53 The patients in the intervention and the control groups were followed up at 3, 6, 12,
54 and 36 months, when they were inquired about their symptoms and daily activities and informed
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4 about available support programmes in their local communities, which they could freely take part
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6 in. Furthermore, health care needs were identified and participants were referred to local health
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8 professionals if necessary.
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10 *Outcomes*

11 Primary outcomes for the patients:

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15 1. Global cognitive function: The patient's global cognitive function was assessed using Mini
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17 Mental State Examination (MMSE).¹³ The sum of scores ranges from 0 to 30. Higher scores
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19 indicate better cognitive function.
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22 2. Depressive symptoms: Cornell Scale for Depression in Dementia was used to assess the
23
24 patient's depressive symptoms through an interview with both the patient and caregiver.¹⁸
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26 The scale has 19 items, each item rating a specific depressive symptom in increasing
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28 severity (0-2), yielding a total score ranging from 0 to 38, with higher scores indicating
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30 more depressive symptoms. A score ≥ 8 indicates significant depressive symptoms and a
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32 score ≥ 10 indicates major depression.
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35 3. Proxy rated quality of life: The primary caregiver evaluated the patient's health-related
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37 quality of life using the EuroQoL EQ-5D,¹⁹ a questionnaire inquiring about mobility, self-
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39 care, activities, pain, discomfort, anxiety, and depression. Quality of life was rated using a
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41 Visual Analogue Scale (EQ-VAS) with scores ranging from 0 to 100 with higher scores
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43 signifying better quality of life.
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46 Primary outcomes for the primary caregivers

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49 1. Depressive symptoms: The caregivers rated their own depressive symptoms using the
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51 Geriatric Depression Scale (GDS).²⁰ The total score ranges from 0 to 30 with higher score
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53 indicating more depressive symptoms. A cut-off score of 10 distinguishes between
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55 depressed and non-depressed individuals.
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2. Self-rated quality of life: The caregivers rated their own health-related quality of life using the EQ-VAS.¹⁹ The scores range from 0 to 100 with high scores indicating good quality of life.

Secondary outcomes for the patients

1. Proxy-rated quality of life, AD-specific: The caregiver rated the patient's quality of life using Quality of Life Scale for Alzheimer's Disease (QoL-AD),²¹ a 13-item scale measuring disease-specific quality of life in people with AD. Total score ranges from 13 to 52 with higher scores indicating better quality of life.
2. Neuropsychiatric symptoms: The patient's neuropsychiatric and behavioural symptoms were assessed through an interview with the caregiver using Neuropsychiatric Inventory-Questionnaire (NPI-Q).²² Total score ranges from 0 to 36 with higher scores indicating more severe disturbances.
3. Activities of daily living: The caregiver completed the Alzheimer's Disease Cooperative Study Activities of Daily Living Scales for clinical trials in Alzheimer's disease (ADCS-ADL)²³ to assess the patient's activities of daily living. ADCS-ADL is a 23-item scale with total scores ranging from 0 to 78. Higher scores indicating better functioning.
4. Mortality and nursing home placement: The Danish Civil Registration System²⁴ was used together with personal contacts with the caregivers to collect information regarding death and nursing home placement. In case of doubt, the local district authority or the residential place was contacted to check if the address was registered as a nursing home.

Baseline and follow-up assessments

Both patients and their caregivers were invited to participate in all the assessments. The local study coordinator carried out the baseline assessment prior to randomisation at the local study centre. Independent raters blind to group assignment carried out 6-, 12- and 36-month follow-

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4 up assessments during home visits. The raters were neither involved in the intervention program nor
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6 employed in the same institutions as the study coordinators. The efficiency of concealment was
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8 checked through questionnaires administered to the raters at the end of each follow-up visit. None
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10 of the raters visited the same patient-caregiver dyad more than once.

11 12 13 **Statistical methods**

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15 Characteristics and outcome measures at baseline of the dyads in the intervention and
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17 control groups were compared using Student's t-tests for continuous variables and χ^2 tests for
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19 categorical variables. With linear models on the full data of up to four observations per dyad, we
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21 compared the difference in development of the primary and secondary outcomes between
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23 randomisation groups during the follow-up period, using generalised estimating equations to
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25 account for repeated measurements; the inclusion of a categorical centre indicator variable account
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27 for possible clustering by treating centre. To adjust for possible bias because of differential death
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29 and dropout from the study between the intervention and control groups, the assessments at the
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31 various follow-up times were weighted by the inverse of an estimate of the probability of staying in
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33 the study.²⁵ These probabilities were estimated from the data in logistic regression models for death
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35 and dropout with the dyads' characteristics and the observed primary outcomes from previous visits
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37 as covariates. Only the expected scores and inferences for the 36-month follow-up were reported.
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39 Differences in mortality and nursing home placement rates between the two groups were evaluated
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41 by a hazard ratio (HR) from a Cox regression model. All analyses were done using the intention-to-
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43 treat principle.
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48 **RESULTS**

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50 558 patients were screened for eligibility and 330 patient-caregiver dyads were
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52 included: 163 were randomized to DAISY intervention group and 167 to control group (Figure 1).
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54 Their demographics, clinical characteristics, and outcome measures at baseline are provided in
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4 Table 1. Most patients received cognition enhancing medications (93.3 % cholinesterase inhibitor
5 and 1% NMDA receptor antagonist).¹ Overall, the participation rate in the DAISY intervention
6 group was high.¹¹
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11 At 36 months, a total of 130 patients (67 in the intervention group and 63 in the
12 control group) were lost to follow up (Figure 1). In all, 56 patients had deceased, 36 from the
13 DAISY intervention group and 20 from the control group (Figure 1). Patients in the DAISY
14 intervention had a higher mortality rate (HR 1.99; 95% CI: 1.15 to 3.43; P = 0.01). Regarding
15 nursing home placement, 43 patients from DAISY intervention group and 48 from the control group
16 were placed in nursing homes at 36-month follow-up. Data on nursing home placement was missing
17 for five participants in the intervention group. There was no difference between the rates of nursing
18 home placement for the intervention and control groups (HR 0.97; 95% CI: 0.64 to 1.47; P = 0.89).
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28 As reported previously, the 12-month follow-up study observed positive trends
29 concerning the effect of DAISY intervention on preventing the emergence of depressive symptoms
30 (Cornell depression scale, primary patient outcome) and maintaining quality of life (proxy-rated
31 QoL-AD, secondary patient outcome).¹¹ In this 36-month follow-up study, which took place after
32 the DAISY interventions had stopped for two years, there was no significant difference in between
33 intervention and control groups regarding these two outcomes (Cornell depression score, P = 0.93;
34 proxy-rated QoL-AD, P = 0.82; Tables 2 and 3). Furthermore, the 36-month follow-up study did not
35 find any long-term effect of DAISY intervention on any of the other primary and secondary
36 outcomes (Tables 2 and 3).
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48 At baseline, the patients were at the very early stage of dementia with a mean MMSE
49 of 24.1 (SD 2.6). At 36-month follow-up, there was a marked fall in MMSE mean scores of 6-7 in
50 both groups, accompanied by a marked deterioration in the patients' quality of life (Table 2).
51 Additionally, the patients were well-functioning in their ADL and had very few behavioural
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4 problems at baseline. At 36-month follow-up, ADL had deteriorated markedly and behavioural
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6 symptoms had emerged (Table 2). Participants in both group had few depressive symptoms at
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8 baseline and minimal changes in mean Cornell Depression Scale scores at 36-month follow-up
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10 compared to baseline (Table 2 and 3).

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12 The study found no effect of DAISY intervention on caregivers' self-rated quality of
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14 life and depressive symptoms at 36-month follow-ups. The caregivers were characterized by lack of
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16 depressive symptoms and a high self-rated quality of life at baseline (Table 1). At 36-month follow-
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18 up, their depressive symptoms and self-rated quality of life had changed minimally from baseline
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20 (Table 2 and 3).

21 22 23 24 **DISCUSSION**

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26 This study did not find any long-term effect of an intensive psychosocial intervention
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28 (DAISY intervention) on patients and caregivers beyond the effect of structured follow-up support.

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30 To our knowledge, this study is the largest randomised controlled trial of early
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32 psychosocial intervention for patients with mild Alzheimer' disease and their caregivers to date,
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34 with a long follow-up of three years. It is a study of solid methodology, strictly adhering to
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36 CONSORT recommendations. A-priori sample size calculation was done. The measures for
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38 primary and secondary outcomes are reliable scales, which are commonly used in routine clinical
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40 practice and in intervention studies across cultures.^{26,27} Proper randomisation, allocation
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42 concealment, rater-blinded evaluation of outcomes, and adjustment for multiple testing were
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44 rigorously carried out to reduce biases that could lead to type I errors.¹¹ The multicomponent semi-
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46 tailored intervention programme was intensive in both content and duration, targeted multiple
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48 needs, tended to the individual needs, and simultaneously involved caregivers and patients; thus
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50 having the characteristics that defined successful intervention programs documented in the
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52 literature.^{2,5,7} Since ours was one of the first studies to examine the effect of support and counselling
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4 programmes in patients with very mild dementia, no previous consensus exists concerning gold
5 standards for assessing efficacy. Therefore, multiple primary and secondary outcomes were
6 exploratively chosen based on the specific aims of the DAISY intervention and on the outcomes
7 from similar intervention studies for patients with more advanced dementia.¹ Consequently, to
8 avoid finding spurious effects, a significance level was set at $P = 0.0005$, which was subsequently
9 criticized for being too conservative.¹² All patients in this study had primary caregivers who were
10 very involved in caregiving, a situation that cannot be generalised to all patients with dementia in
11 Denmark.

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22 Although not statistically significant for this P value, DAISY intervention did
23 produce small positive trends on reducing depressive symptoms (Cornell depression score,
24 $P=0.0103$) and maintaining quality of life for the patients (proxy rated QoL-AD, $P=0.0013$) at 12-
25 month follow-up.¹¹ The disease-specific QoL-AD is probably more sensitive to measure the effect
26 of psychological interventions than general EQ-VAS.²⁷ At 36-month follow-up, these positive
27 trends were no longer present (Cornell depression score, $P = 0.93$; proxy-rated QoL-AD, $P = 0.82$).
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Between 12- and 36-month follow-up, there was significant decline in patients' cognition, quality of
life, and ADL. During this time period, there was no continuing intervention or support. Initially,
the study was intended to end at 12-month follow-up. However, we received additional funding to
carry out follow-up at 36 months. The timing and duration of DAISY intervention could have
missed a period of significant decline when intervention could have been more beneficial. Possibly,
the positive trends observed at the 12-month follow-up could have been maintained or enhanced
had the intervention continued an additional two years. Evidence from the very limited literature
seems to support the hypothesis that the positive effects of psychosocial interventions could be lost
without continuous reinforcement. There are few randomised controlled trials assessing the efficacy
of psychosocial intervention that specifically targets community-dwelling patients with

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4 dementia.^{6,10} Most trials had short follow-up period, usually three to six months. One trial showed
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6 that a three-month programme of intensive physical exercise for the patients combined with
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8 teaching caregivers strategies to manage patients' behavioural problems improved the patients'
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10 physical functioning and depressive symptoms.²⁸ At 24-month follow-up, the improvement in
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12 physical functioning was still significant, but the improvement of depressive symptoms was no
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14 longer present.²⁸ In contrast, another trial with eight-year follow-up reported delayed nursing home
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16 placement for patients by providing a multicomponent interventions for the caregivers and patients;
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18 the ten-day intervention program was followed by continuous support over the telephone weekly for
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20 the first year and yearly thereafter for the next seven years.²⁹
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24 In our study, there are some possible explanations for the non-significant positive
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26 effects found at 12-month concerning patients' depressive symptoms and quality of life and the
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28 disappearance of these effects at 36-month follow-up. First, it could be a floor effect. Our patients
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30 had minimal depressive symptoms and relatively high scores of QoL-AD at baseline. A randomised
31
32 controlled trial using support group intervention for community-dwelling patients with mild
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34 Alzheimer's disease and their caregivers showed that patients who experienced improvement in
35
36 their depressive symptoms had significantly more depressive symptoms at baseline and higher level
37
38 of distress.³⁰ Second, there was no need assessment at baseline. Probably, participants with more
39
40 symptoms and at greater need should have received the full intensive intervention programme and
41
42 regular support follow-up was sufficient for those who had minimal symptoms and needs at
43
44 baseline. Third, the control group also received some intervention that is much better than the usual
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46 practice in Denmark.³¹ They had regular follow-ups when they could speak about emerging
47
48 psychosocial and health problems, receive information about available resources, and get referred to
49
50 relevant health professionals if needed. It is noteworthy that despite the marked decline in patients'
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52 global cognitive function, quality of life, and ADL between 12- and 36-month follow-ups,
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4 participants in both group had minimal changes in mean Cornell Depression Scale scores compared
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6 to baseline. This could be an indication that the regular follow-ups offered in this study were
7
8 sufficient enough to produce a long-term effect in preventing the conversion into clinical depression
9
10 for the patients. Fourth, as mentioned above, the intervention should probably continue
11
12 longitudinally following the clinical progression in these patients to show long-term positive
13
14 effects. The study did not find any long-term effect on DAISY intervention on the caregiver
15
16 outcomes. Previous studies have shown positive responses to interventions from caregivers with
17
18 high levels of depression and anxiety at baseline.¹⁰ For this mostly asymptomatic group of
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20 caregivers in our study, perhaps follow-up at regular intervals provided enough information and
21
22 support to prevent the emergence of depressive symptoms and maintain good life quality.
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26 Patients in the intervention group had higher mortality than those in the control group.
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28 This increased mortality was unlikely to be caused by the intervention, as the nature of the
29
30 intervention program did not subject the patients to any health risk. Using the data from Statistics
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32 Denmark (www.dst.dk), the incidence of death for the age-matched general population over the
33
34 same time period was found to be similar to that of the DAISY intervention group. The control
35
36 group however had lower incidence of death compared to the general population. At baseline, the
37
38 quality of life of the patients in the intervention group was rated as poorer than that of the control
39
40 group, both by the patients themselves and by their caregivers (Table 1). Although not statistically
41
42 significant, there were socioeconomic and clinical differences that were in favour of the control
43
44 group. More patients in the intervention group lived alone (4% difference), rented their house (7%
45
46 difference), had more co-morbidities (4.4% difference), and were diagnosed with mixed AD and
47
48 vascular dementia (4.2% difference, Table 1). Whether these differences could contribute to the
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50 higher mortality in the intervention group is uncertain. It is known that older people living alone
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52 have higher mortality than those living with others.³² Currently, there is insufficient evidence in the
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4 literature concerning the effect of psychosocial intervention on patient mortality, as studies looking
5 at this effect are scarce.^{5,33} The same patient characteristics in the DAISY intervention group stated
6 above could also explain the lack of effect concerning nursing home placement.³⁴ Additionally,
7
8 continuous intervention and follow-up between 12 and 36 months could have been needed to
9
10 produce a positive long-term effect on nursing home placement. Randomised controlled trials that
11 reported positive long-term effect of psychosocial intervention on patients' nursing home placement
12 provided continuous support and counselling over the phone for eight-nine years.^{29,35} In contrast,
13 intervention lasting two years but without continuous follow-up and support showed no long-term
14 effect on nursing home placement.³³

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24 Although this study found no long-term effect of DAISY intervention, a qualitative
25 study linked to this randomised controlled trial showed promising indications that early
26 psychosocial intervention for patient with very mild Alzheimer's disease and their caregivers could
27 potentially prevent the emergence of depressive symptoms and maintain the quality of life for the
28 patients.³⁶ This study revealed that both patients and caregivers found the DAISY intervention
29 stimulating and rewarding. Patients felt that their self-esteem was improved and they could better
30 manage their daily life and social relations. Caregivers felt that they were more confident and
31 competent to cope with the challenges of caring for relatives with AD. After the intervention, both
32 patients and caregivers looked for support groups to join permanently and caregivers sought
33 continuing counseling.³⁶ The lessons learned from this study is that the content, dose and intensity,
34 and duration of early intervention can be more tailored to match the needs of patients and their
35 caregivers at baseline to maximize benefit, economize resources, and avoid unnecessary
36 intervention burden. Need assessment is of primary importance. The intervention program should
37 perhaps be designed so that patients and caregivers with greater needs at baseline receive more
38 intensive interventions that cater to their specific needs, those with lesser needs receive a basic
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4 intervention program of lower intensity, and those with minimal or no needs receive no intervention
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6 at all. Regular follow-up assessment is necessary to identify emerging needs. To obtain long-term
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8 effect, early intervention should probably have a longitudinal and fluid course that follows the
9
10 disease progression, being continuously modified according to the needs that arise. These are the
11
12 questions to be answered in future studies.

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Figure 1: Trial flow for Danish Alzheimer Intervention Study (DAISY)

¹ Patients and caregivers. ² Full compliance is defined as participation from both the caregiver and the patient in at least 3 courses and 3 counselling sessions each. ³ In the analysis accounting for drop outs, information from all participating dyads were incorporated.

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Table 1: Baseline characteristics of patients with Alzheimer's disease and their caregivers who participated in the Danish Alzheimer Intervention Study (DAISY). Values are numbers (percentages) of participants unless stated otherwise

Patients' characteristics	Intervention (n=163)	Control (n=167)
Sex		
Male	76 (46.6)	75 (44.9)
Female	87 (53.4)	92 (55.1)
Mean (SD) age (years)	76.5 (7.7)	75.9 (6.6)
Household status		
Living alone	54 (33.1)	48 (28.7)
Living with others	109 (66.9)	119 (71.3)
Home		
Rented	66 (40.5)	56 (33.5)
Owned	97 (59.5)	111 (66.5)
Education		
None	60 (36.8)	57 (34.1)
< 3 years	39 (23.9)	49 (29.3)
≥ 3 years	64 (39.3)	61 (36.5)
Charlson comorbidity index		
No comorbidity	64 (39.3)	73 (43.7)
One comorbidity	75 (46.0)	65 (38.9)
≥ 2 comorbidities	24 (14.7)	29 (17.4)
Diagnosis		
Pure Alzheimer's disease	112 (68.7)	127 (76.1)
Mixed Alzheimer's disease and vascular dementia	44 (27.0)	38 (22.8)
Lewy body dementia	7 (4.3)	2 (1.2)
Caregiver' characteristics		
Sex		
Male	54 (33.1)	56 (33.5)
Female	109 (66.9)	111 (66.5)
Mean (SD) age (years)	65.5 (12.7)	66.5 (12.7)
Relation		
Spouse	104 (63.8)	111 (66.5)
Child or child in law	45(27.6)	41(24.5)
Other	14 (8.6)	15 (9.0)
Living with patient		
Yes	101/162 (62.4)	112/166 (67.5)
No	61/162 (37.6)	54/166 (32.5)
Home		
Rent	45 (27.6)	45 (26.9)
Own	118 (72.4)	122 (73.1)
Education		

None	41 (25.2)	37/166 (22.3)
< 3 years	46 (28.2)	63/166 (37.9)
≥ 3 years	76 (46.6)	66 /166 (39.8)
Outcome measures at baseline		
Primary patient outcomes		
Mean (SD) MMSE	24.0 (2.5)	24.1 (2.7)
Mean (SD) Cornell Depression Scale	5.2 (4.8)	4.4 (4.0)
Mean (SD) proxy-rated EQ-VAS	62.1 (18.4) (n=162)	64.7 (20.4)
Primary caregiver outcome		
Mean (SD) EQ-VAS	79.3 (16.3) (n=162)	81.4 (16.3)
Mean (SD) GDS	4.74 (5.2) (n=162)	4.71 (5.0)
Secondary patient outcome		
Mean (SD) QoL-AD (proxy-rated)	33.0 (6.1)	34.7 (6.6)
Mean (SD) NPI-Q	3.9 (3.6)	3.9 (3.7)
Mean (SD) ADSC-ADL	61.2 (11.4)	61.8 (11.4)

MMSE: Mini Mental State Examination. EQ-VAS: European Quality of Life Visual Analogue Scale. GDS: Geriatric Depression Scale. QoL-AD: Quality of Life Scale for Alzheimer's Disease. NPI-Q: Neuropsychiatric Inventory Questionnaire. ADSC-ADL: Alzheimer's Disease Cooperative Study Activities of Daily Living Scale.

Table 2: Outcome measures of DAISY psychosocial interventions based on completed response at 36-month follow-up. Values are means (SD) unless stated otherwise.

	Observed scores		Changes from baseline	
	Intervention	Control	Intervention	Control
Primary patient outcomes				
MMSE	17.8 (6.7) (n=84)	17.9 (7.1) (n=94)	-6.21 (6.17) (n=84)	-6.35 (6.26) (n=94)
Cornell Depression Scale	5.57 (4.78) (n=93)	5.17 (4.19) (n=101)	1.29 (4.94) (n=93)	0.74 (4.45) (n=101)
Proxy-rated EQ-VAS	50.7 (20.3) (n=95)	52.3 (21.0) (n=102)	-12.88 (20.3) (n=95)	-12.46 (19.0) (n=102)
Primary caregiver outcomes				
EQ-VAS	79.4 (16.1) (n=94)	79.0 (18.0) (n=103)	-0.79 (16.5) (n=94)	-1.49 (16.5) (n=103)
GDS	5.26 (5.43) (n=94)	4.51 (5.26) (n=103)	0.81 (4.83) (n=94)	0.14 (4.52) (n=103)
Secondary patient outcomes				
QoL-AD (proxy-rated)	30.5 (5.1) (n=96)	32.1 (6.2) (n=103)	-2.89 (4.89) (n=96)	-2.84 (-2.00) (n=103)
NPI-Q	5.21 (4.43) (n=96)	5.05 (4.80) (n=104)	1.57 (4.43) (n=96)	1.20 (4.68) (n=104)
ADSC-ADL	35.3 (19.4) (n=96)	41.3 (20.8) (n=104)	-26.7 (16.6) (n=96)	-22.3 (19.6) (n=104)

MMSE: Mini Mental State Examination. EQ-VAS: European Quality of Life Visual Analogue Scale. GDS: Geriatric Depression Scale. QoL-AD: Quality of Life Scale for Alzheimer's Disease. NPI-Q: Neuropsychiatric Inventory Questionnaire. ADSC-ADL: Alzheimer's Disease Cooperative Study Activities of Daily Living Scale.

Table 3: Outcomes of DAISY psychosocial interventions based on inverse probability weighting of respondents with non-missing data at 36-month follow up (intention to treat analyses adjusted for attrition). Values are means* (95% CI) unless stated otherwise.

	Estimated endpoint scores			Mean change from baseline		
	Intervention	Control	P value of t test	Intervention	Control	P value of t test
Primary patient outcomes:						
MMSE	18.0 (16.5 to 19.6)	18.1 (16.4 to 19.8)	0.96	-6.57 (-7.89 to -5.25)	-6.56 (-7.98 to -5.14)	0.99
Cornell Depression Scale	4.89 (3.75 to 6.03)	4.20 (3.10 to 5.31)	0.32	0.59 (-0.49 to 1.66)	0.64 (-0.21 to 1.49)	0.93
Proxy-rated EQ-VAS	55.9 (51.0 to 60.8)	60.1 (54.6 to 65.6)	0.20	-12.44 (-16.64 to -8.24)	-10.77 (-15.19 to -6.35)	0.59
Primary caregiver outcome						
EQ-VAS	80.3 (76.2 to 84.3)	79.5 (74.5 to 84.6)	0.78	0.14 (-3.18 to 3.47)	-2.71 (-6.66 to 1.23)	0.28
GDS	5.83 (4.27 to 7.38)	4.98 (3.43 to 6.53)	0.29	0.47 (-0.58 to 1.52)	-0.33 (-1.39 to 0.72)	0.29
Secondary patient outcome						
QoL-AD (proxy-rated)	31.0 (29.3 to 32.6)	32.8 (31.2 to 35.3)	0.03	-2.83 (-3.85 to -1.80)	-2.64 (-3.82 to -1.46)	0.82
NPI-Q	4.90 (3.85 to 5.96)	4.73 (3.53 to 5.93)	0.79	1.48 (0.55 to 2.40)	1.30 (0.37 to 2.23)	0.80
ADSC-ADL	34.1 (29.1 to 39.2)	39.9 (35.1 to 44.7)	0.05	-26.9 (-30.8 to -22.9)	-21.7 (-25.6 to -17.7)	0.07

MMSE: Mini Mental State Examination. EQ-VAS: European Quality of Life Visual Analogue Scale. GDS: Geriatric Depression Scale. QoL-AD: Quality of Life Scale for Alzheimer's Disease. NPI-Q: Neuropsychiatric Inventory Questionnaire. ADSC-ADL: Alzheimer's Disease Cooperative Study Activities of Daily Living Scale.

*Means are estimated from a longitudinal model where selective dropout is accounted for by inverse probability weighting; the inclusion of a categorical indicator variable for treating centre accounts for possible clustering within centre; confidence intervals and P values are calculated with generalised estimating equations.

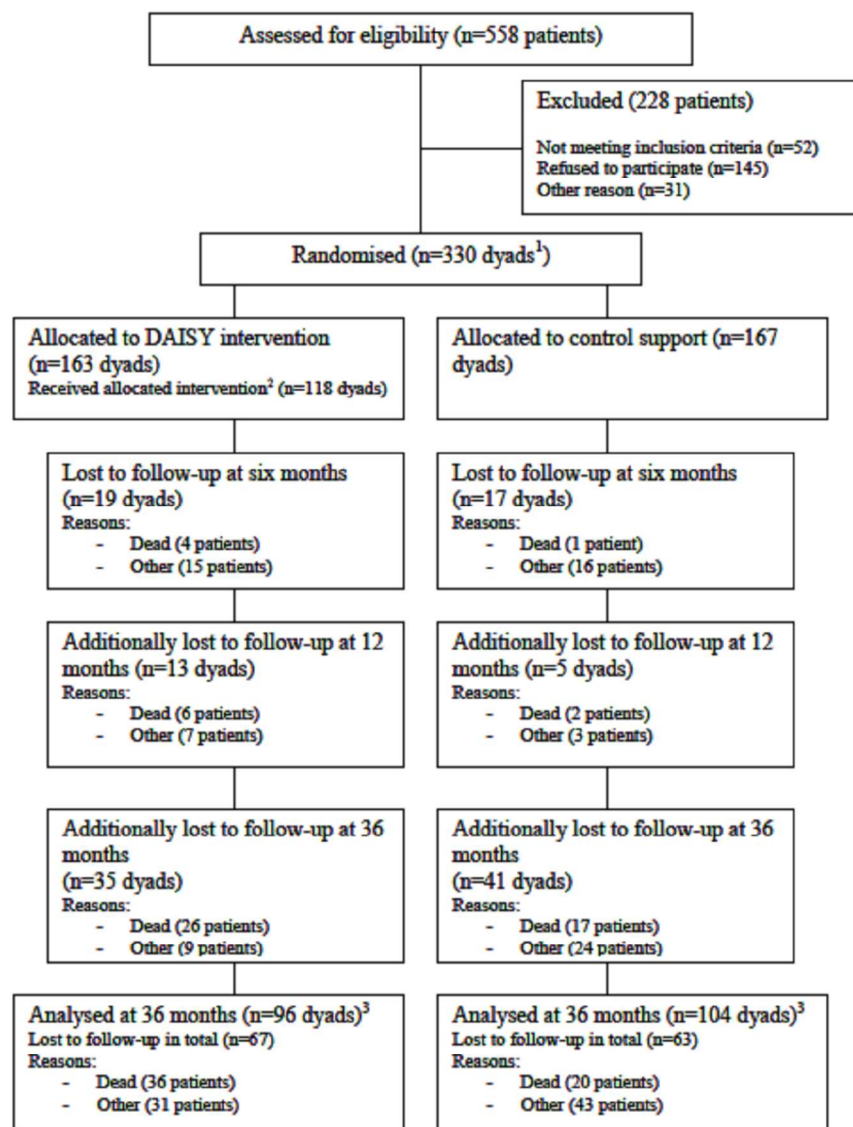


Figure 1: Trial flow for Danish Alzheimer Intervention Study (DAISY)
396x486mm (96 x 96 DPI)

Table 2 (alternative): Outcome of DAISY psychosocial interventions based on completed response at 36-month follow-up. All analyses were intention-to-treat.

	Observed scores		Change from baseline		Differences in scores, intervention versus control*	
	Intervention	Control	Intervention	Control	Mean (95%CI)	P-value
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)		
Primary patient outcomes						
MMSE	17.8 (6.7) (n=84)	17.9 (7.1) (n=94)	-6.21 (6.17) (n=84)	-6.35 (6.26) (n=94)	0.19 (-2.30 to 2.71)	0.89
Cornell Depression Scale	5.57 (4.78) (n=93)	5.17 (4.19) (n=101)	1.29 (4.94) (n=93)	0.74 (4.45) (n=101)	0.47 (-0.68 to 1.61)	0.42
EQ-VAS (proxy-rated)	50.7 (20.3) (n=95)	52.3 (21.0) (n=102)	-12.88 (20.3) (n=95)	-12.46 (19.0) (n=102)	-0.95 (-3.97 to 2.07)	0.54
Primary caregiver outcome						
EQ-VAS	79.4 (16.1) (n=94)	79.0 (18.0) (n=103)	-0.79 (16.5) (n=94)	-1.49 (16.5) (n=103)	0.53 (-2.08 to 3.15)	0.69
GDS	5.26 (5.43) (n=94)	4.51 (5.26) (n=103)	0.81 (4.83) (n=94)	0.14 (4.52) (n=103)	0.70 (-0.31 to 1.70)	0.17
Secondary patient outcome						
QoL-AD (proxy-rated)	30.5 (5.1) (n=96)	32.1 (6.2) (n=103)	-2.89 (4.89) (n=96)	-2.84 (-2.00) (n=103)	-0.70 (-1.57 to 0.16)	0.11
NPI-Q	5.21 (4.43) (n=96)	5.05 (4.80) (n=104)	1.57 (4.43) (n=96)	1.20 (4.68) (n=104)	0.27 (-0.59 to 1.13)	0.54
ADSC-ADL	35.3 (19.4) (n=96)	41.3 (20.8) (n=104)	-26.7 (16.6) (n=96)	-22.3 (19.6) (n=104)	-4.74 (-8.12 to -1.35)	0.01

MMSE: Mini Mental State Examination. EQ-VAS: European Quality of Life Visual Analogue Scale. GDS: Geriatric Depression Scale. QoL-AD: Quality of Life Scale for Alzheimer's Disease. NPI-Q: Neuropsychiatric Inventory Questionnaire. ADSC-ADL: Alzheimer's Disease Cooperative Study Activities of Daily Living Scale.

*The mean difference in outcome attributable to the randomisation is assessed in an analysis of covariance where the primary comparison between randomisation groups is adjusted for the baseline value of the corresponding outcome in a multivariable linear regression model; the confidence intervals (95% CI) and P-values corresponding to these differences are calculated using generalised estimating equations to account for correlation within treating centre.



CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	5
	2b	Specific objectives or hypotheses	6
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	6
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	NA
Participants	4a	Eligibility criteria for participants	7
	4b	Settings and locations where the data were collected	7
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	7
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	8,9,10
	6b	Any changes to trial outcomes after the trial commenced, with reasons	NA
Sample size	7a	How sample size was determined	6
	7b	When applicable, explanation of any interim analyses and stopping guidelines	NA
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	6
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	6
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	6,11
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	6,7
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	6,10,11

1			
2		assessing outcomes) and how	
3			
4		11b If relevant, description of the similarity of interventions	
5	Statistical methods	12a Statistical methods used to compare groups for primary and secondary outcomes	11
6		12b Methods for additional analyses, such as subgroup analyses and adjusted analyses	11
7			
8	Results		
9	Participant flow (a	13a For each group, the numbers of participants who were randomly assigned, received intended treatment, and	Figure 1
10	diagram is strongly	were analysed for the primary outcome	
11	recommended)	13b For each group, losses and exclusions after randomisation, together with reasons	Figure 1,
12	Recruitment	14a Dates defining the periods of recruitment and follow-up	
13		14b Why the trial ended or was stopped	7
14			
15	Baseline data	15 A table showing baseline demographic and clinical characteristics for each group	Table 1
16	Numbers analysed	16 For each group, number of participants (denominator) included in each analysis and whether the analysis was	
17		by original assigned groups	Table 2
18			
19	Outcomes and	17a For each primary and secondary outcome, results for each group, and the estimated effect size and its	
20	estimation	precision (such as 95% confidence interval)	Table 3,
21			pages 11-13
22		17b For binary outcomes, presentation of both absolute and relative effect sizes is recommended	NA
23	Ancillary analyses	18 Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing	Table 2 and 3
24		pre-specified from exploratory	
25			
26	Harms	19 All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	12,16
27			
28	Discussion		
29	Limitations	20 Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	13,14
30	Generalisability	21 Generalisability (external validity, applicability) of the trial findings	14
31	Interpretation	22 Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	14,15,16,17
32			
33	Other information		
34	Registration	23 Registration number and name of trial registry	1
35	Protocol	24 Where the full trial protocol can be accessed, if available	6
36	Funding	25 Sources of funding and other support (such as supply of drugs), role of funders	19
37			

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.



Three-year follow-up on the efficacy of psychosocial interventions for patients with mild dementia and their caregivers: the multicentre, rater blinded, randomized Danish Alzheimer Intervention Study (DAISY)

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4 **Three-year follow-up on the efficacy of psychosocial interventions for patients with mild**
5 **dementia and their caregivers: the multicentre, rater blinded, randomised Danish Alzheimer**
6 **Intervention Study (DAISY)**
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8
9

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28 Trial registration: The study was registered in the Clinical Trial Database ([www.controlled-](http://www.controlled-trials.com/ISRCTN74848736)
29 [trials.com/ISRCTN74848736](http://www.controlled-trials.com/ISRCTN74848736)).
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Abstract

Objectives: To examine the long-term efficacy at 36-month follow-up of an early psychosocial counselling and support programme lasting 8-12 months for community-dwelling patients with mild Alzheimer's disease and their caregivers.

Design: Multicentre, randomised, controlled, rater-blinded trial.

Setting: Primary care and memory clinics in five Danish districts.

Participants: 330 home-dwelling patients with mild Alzheimer's disease and their primary caregivers (dyads).

Interventions: Dyads were randomized to receive intervention during the first year after diagnosis. Both intervention and control groups had follow-up visits at 3, 6, 12, and 36 months.

Main outcome measures: Primary outcomes for the patients assessed at 36-month follow-up were changes from baseline in global cognitive function (Mini Mental State Examination), depressive symptoms (Cornell Depression Scale), and proxy rated EuroQoL quality of life on visual analogue scale. The primary outcomes for the caregivers were changes from baseline in depressive symptoms (Geriatric Depression Scale) and self-rated EuroQoL quality of life on visual analogue scale. The secondary outcome measures for the patient were proxy rated Quality of Life Scale for Alzheimer's Disease (QoL-AD), Neuropsychiatric Inventory-Questionnaire, Alzheimer's Disease Cooperative Study Activities of Daily Living Scale, all-cause mortality, and nursing home placement.

Results: At 36-month follow-up, two years after the completion of the DAISY intervention, the unadjusted positive effects previously detected at 12-month follow-up in one patient primary outcome (Cornell depression score) and one patient secondary outcome (proxy-rated QoL-AD) disappeared (Cornell depression score, $P = 0.93$; proxy-rated QoL-AD, $P = 0.81$). No long-term effect of DAISY intervention on any other primary and secondary outcomes at 36-month follow-up was found.

Conclusions:

For patients with very mild Alzheimer's disease and their caregivers, an intensive, multicomponent, semi-tailored psychosocial intervention program with counselling, education, and support during the first year after diagnosis did not show any positive long-term effect on primary and secondary outcomes.

Article summary

Article focus:

- Psychosocial intervention for caregivers of patients with Alzheimer's disease has been shown to have beneficial effects on patients' and caregivers' psychological morbidity. Results are inconsistent concerning nursing home placement of the patients. Studies with psychosocial intervention for both patients and caregivers are scarce. Few have targeted patients with very mild Alzheimer's disease. In general, there is a lack of long-term follow up beyond 12 months.
- It was hypothesized that the DAISY (Danish Alzheimer Intervention Study) interventions, a multifaceted and semi-tailored intervention programme offered to patients with AD and their primary caregivers during the first year after the diagnosis, could have a long-term effect in preventing the emergence of depressive symptoms, improving quality of life for the patients and the caregivers, stabilising the patients' cognitive function, and delaying nursing home placement

Key messages

- An intensive, multicomponent, semi-tailored psychosocial intervention program with counselling, education, and support to patients with very mild Alzheimer's disease and their caregivers during the first year after diagnosis did not improve the three-year outcomes

concerning patients' and caregivers' psychological morbidity and patients' nursing home placement compared to structured and systematic follow-up support.

- To maximize benefit, economize resources, and avoid unnecessary intervention burden, the needs of patients with very mild dementia their caregivers should probably be assessed to determine whether psychosocial intervention is necessary and tailor the intervention modalities accordingly. Regular reassessments probably are needed to identify emerging needs and modify the interventions longitudinally.

Strengths and limitations

- This is the largest randomised controlled trial of early psychosocial intervention for patients with mild Alzheimer' disease and their caregivers to date, with a long follow-up of three years.
- It is a study of solid methodology, strictly adhering to CONSORT recommendations.
- The multicomponent semi-tailored intervention programme was intensive in both content and duration, targeted multiple needs, tended to the individual needs, and simultaneously involved caregivers and patients; thus having the characteristics that defined successful intervention programs documented in the literature.
- Multiple primary and secondary outcomes were chosen based on the specific aims of the DAISY intervention and on the outcomes from similar intervention studies for patients with more advanced dementia. To avoid finding spurious effects, a conservative significance level was set at $P = 0.0005$.
- All patients had primary caregivers who are very involved in caregiving, a situation that cannot be generalised to all patients with dementia in Denmark.
- There was no need assessment at baseline.

- Intervention lasted one year but without continuous follow-up and support during the subsequent two years.

INTRODUCTION

Psychosocial interventions for patients with Alzheimer's disease (AD) and their caregivers have gained recognition during the last two decades. The majority of patients with dementia live in their own homes with their caregivers, usually their spouses, who bear the responsibility of caregiving.¹ Caring for family members with dementia has long been considered as the most stressful type of family caregiving, predisposing caregivers to mental and physical illnesses and increasing their risk for death.² Previously an under-researched area, the needs of patients with AD have received more attention in recent years, with studies documenting their needs for information about their illness, for help to cope with their disabilities, for social recognition and support, and for a decent quality of life with meaningful social contact and activities.³ Patients' unmet needs can result in mood and behavioural problems, safety issues, social isolation, and increased risk for nursing home placement and death.⁴ Meta-analyses and systematic reviews of the numerous clinical trials assessing the efficacy of psychosocial interventions for caregivers have shown a significant effect of interventions on reducing caregivers' psychological morbidity and reduce patients' neuropsychiatric symptoms.^{5,6,7,8,9} Studies examining the effect of psychosocial intervention on patients' mortality and nursing home placement are scarce and the results are inconsistent.^{5,10} Studies that included psychosocial interventions for the patients are limited, providing anecdotal evidence for positive effects of interventions on patients' cognitive function, psychological morbidity, and time to nursing home placement.¹⁰ Today, thanks to the remarkable advances in diagnosing dementia, patients can be diagnosed at an early stage when their relatively intact autonomy and insight enable them to convey their needs and actively participate in

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4 intervention programmes. The rapidly growing number of people with AD in the coming years, a
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6 considerable proportion of them diagnosed in the early stages, presents a pressing need to develop
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8 and validate intervention programmes that focus on the needs of patients with mild dementia and
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10 their caregiver and involve both parties in the intervention.
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13 It was hypothesized that the DAISY (Danish Alzheimer Intervention Study)
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15 interventions, a multifaceted and semi-tailored intervention programme offered to patients with AD
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17 and their primary caregivers during the first year after the diagnosis, could have a long-term effect
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19 in preventing the emergence of depressive symptoms, improving quality of life for the patients and
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21 the caregivers, stabilising the patients' cognitive function, and delaying nursing home placement.¹
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23 The results of the 12-month follow-up were published in BMJ in 2012, showing no significant
24
25 difference in outcomes between the DAISY intervention and the control groups.¹¹ However, the
26
27 significant level corrected for multiple testing ($P=0.0005$) was subsequently criticized for being too
28
29 conservative, given that an alternative correction method could have given another conclusion.¹²
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31 Before adjustment for multiple testing was carried out, the data analysis of the results at 12-month
32
33 follow-up had shown statistical significance in one primary patient outcome (Cornell depression
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35 Scale score, $P = 0.0103$) and one secondary patient outcome (proxy-rated quality of life QoL-AD, P
36
37 = 0.0013) in favour of the DAISY intervention group.¹¹ Therefore, a 36-month follow-up was
38
39 subsequently carried out to follow the evolution of these outcomes. This paper reports on the results
40
41 of this follow-up.
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45 46 **METHODS**

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48 Detailed description of the study rationale, methods, design, randomisation, and
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50 sample size has been published.¹
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Trial Design

DAISY was a large multicentre, rater blinded, one-year randomised controlled trial of the efficacy of intensive psychosocial intervention for patients with mild AD and their caregivers. It was an exploratory randomised clinical trial with multiple primary and secondary outcomes.

Participants

The patients were recruited from five Danish districts. One designated memory clinic in each district recruited the patients for the trial. Each recruiting centre had one study coordinator and one physician who assessed the patients for eligibility. Patients were referred from local memory clinics as well as private practice in psychiatry, neurology, geriatrics and family medicine. If referred from private practice, dementia diagnosis was confirmed by specialists in the recruiting memory clinic.

The inclusion criteria were: 1) Home living patients diagnosed within the past 12 months with AD, mixed AD with vascular component, or Lewy body dementia, 2) 50 years of age or older, 3) Mini Mental State Examination (MMSE) score ≥ 20 ,¹³ and 4) having one participating primary caregiver. The primary caregiver was defined as the main person responsible for the informal care of the patient with minimum weekly contact. All patients met DSM-IV criteria for dementia,¹⁴ NINCDS-ADRDA criteria for probable Alzheimer's disease,¹⁵ or McKeith criteria for Lewy Body dementia.¹⁶ Patients with mixed Alzheimer's disease were those with probable Alzheimer's disease and minor vascular changes on cranial CT that could contribute to their symptoms.

Patients with severe somatic or psychiatric co-morbidities (including impaired hearing or vision) that would significantly impair their compliance with the DAISY intervention programme were excluded. Patients who had already been involved in other intervention programmes were also excluded. Patient-caregiver dyads were randomised to the DAISY intervention group, in which they

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4 were provided with intensive psychosocial interventions and follow-up support at 3, 6, and 12
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6 months; or to the control group, in which they were only provided with follow-up support at 3, 6,
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8 and 12 months. The study was subsequently extended and the patients and their caregivers were
9
10 asked to give a separate consent to an additional follow-up at 36 months.

11 12 *Intervention*

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15 A multifaceted and semi-tailored psychosocial intervention programme, described in
16
17 details in our previous reports,^{1,11} was designed to provide counselling, information, and support to
18
19 patients with mild dementia and their caregivers in the intervention group. The study coordinator in
20
21 each centre, an experienced nurse specialising in caring for patients with dementia and having
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23 received special training in counselling for the study (constructivist approach),¹⁷ implemented the
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25 intervention within the first month after inclusion in the trial. Consisting of five key components,
26
27 the intervention focused on positive resources, intact function, retained skills, and feasible activities
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29 for the patients: 1) The study coordinator provided seven individual counselling sessions tailored to
30
31 the needs of the patients and their caregivers: two for the patient alone, two for the caregiver alone,
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33 two for the patient-caregiver dyad, and one with the dyad together with their family network
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35 (optional); 2) The study coordinator provided outreach telephone counselling 5-8 times with 3-4
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37 week intervals to maintain regular contact and follow up on the individual counselling sessions; 3)
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39 Using log books, the patients and their caregivers independently kept track of the thoughts and daily
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41 issues that they wanted to discuss at the counselling sessions; 4) Experts in the field of dementia
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43 were invited to teach five standard courses as group intervention with separate courses for patients
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45 and caregivers to provide general information about dementia and forum for discussion, sharing
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47 information, and support; 5) Patients and caregivers were provided with information folders
48
49 produced especially for the purpose of the study about dementia causes, diagnosis and treatment,
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51 legal issues, and resources for social support. The intervention program lasted 8 to 12 months. Full
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4 compliance was defined as adherence with the major components of the intervention program:
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6 Patients who participated with their caregivers in at least 3 counselling sessions (not including the
7
8 optional network session) and in at least 3 teaching course sessions.
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11 The patients in both the intervention and the control groups were followed up at 3, 6,
12
13 12, and 36 months. Attempts were made to provide similar treatment for both intervention and
14
15 control participants in all respects other than the add-on DAISY intervention. At each follow-up
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17 visit, participants in both groups were interviewed about their current symptoms and daily life
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19 issues, and informed about available support program (if any) in their local communities. Both
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21 groups were free to participate in such support programs during the study and participation in these
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23 support activities was registered for both groups. Identified special needs led to referral to local care
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25 facilities when available and relevant.
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28 *Outcomes*

29 Primary outcomes for the patients:

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- 33 1. Global cognitive function: The patient's global cognitive function was assessed using Mini
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35 Mental State Examination (MMSE).¹³ The sum of scores ranges from 0 to 30. Higher scores
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37 indicate better cognitive function.
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 - 39 2. Depressive symptoms: Cornell Scale for Depression in Dementia was used to assess the
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41 patient's depressive symptoms through an interview with both the patient and caregiver.¹⁸
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43 The scale has 19 items, each item rating a specific depressive symptom in increasing
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45 severity (0-2), yielding a total score ranging from 0 to 38, with higher scores indicating
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47 more depressive symptoms. A score ≥ 8 indicates significant depressive symptoms and a
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49 score ≥ 10 indicates major depression.
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 - 52 3. Proxy rated quality of life: The primary caregiver evaluated the patient's health-related
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54 quality of life using the EuroQoL EQ-5D,¹⁹ a questionnaire inquiring about mobility, self-
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care, activities, pain, discomfort, anxiety, and depression. Quality of life was rated using a Visual Analogue Scale (EQ-VAS) with scores ranging from 0 to 100 with higher scores signifying better quality of life.

Primary outcomes for the primary caregivers

1. Depressive symptoms: The caregivers rated their own depressive symptoms using the Geriatric Depression Scale (GDS).²⁰ The total score ranges from 0 to 30 with higher score indicating more depressive symptoms. A cut-off score of 10 distinguishes between depressed and non-depressed individuals.
2. Self-rated quality of life: The caregivers rated their own health-related quality of life using the EQ-VAS.¹⁹ The scores range from 0 to 100 with high scores indicating good quality of life.

Secondary outcomes for the patients

1. Proxy-rated quality of life, AD-specific: The caregiver rated the patient's quality of life using Quality of Life Scale for Alzheimer's Disease (QoL-AD),²¹ a 13-item scale measuring disease-specific quality of life in people with AD. Total score ranges from 13 to 52 with higher scores indicating better quality of life.
2. Neuropsychiatric symptoms: The patient's neuropsychiatric and behavioural symptoms were assessed through an interview with the caregiver using Neuropsychiatric Inventory-Questionnaire (NPI-Q).²² Total score ranges from 0 to 36 with higher scores indicating more severe disturbances.
3. Activities of daily living: The caregiver completed the Alzheimer's Disease Cooperative Study Activities of Daily Living Scales for clinical trials in Alzheimer's disease (ADCS-ADL)²³ to assess the patient's activities of daily living. ADCS-ADL is a 23-item scale with total scores ranging from 0 to 78. Higher scores indicating better functioning.

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4 4. Mortality and nursing home placement: The Danish Civil Registration System²⁴ was used
5 together with personal contacts with the caregivers to collect information regarding death
6 and nursing home placement. In case of doubt, the local district authority or the residential
7 place was contacted to check if the address was registered as a nursing home.
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12 *Baseline and follow-up assessments*

13 Both patients and their caregivers were invited to participate in all the assessments.
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15 The local study coordinator carried out the baseline assessment prior to randomisation at the local
16 study centre. Independent raters blind to group assignment carried out 6-, 12- and 36-month follow-
17 up assessments during home visits. The raters were neither involved in the intervention program nor
18 employed in the same institutions as the study coordinators. The efficiency of concealment was
19 checked through questionnaires administered to the raters at the end of each follow-up visit. None
20 of the raters visited the same patient-caregiver dyad more than once.
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30 **Statistical methods**

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33 Characteristics and outcome measures at baseline of the dyads in the intervention and
34 control groups were compared using Student's t-tests for continuous variables and χ^2 tests for
35 categorical variables. With linear models on the full data of up to four observations per dyad, we
36 compared the difference in development of the primary and secondary outcomes between
37 randomisation groups during the follow-up period, using generalised estimating equations to
38 account for repeated measurements; the inclusion of a categorical centre indicator variable account
39 for possible clustering by treating centre. To adjust for possible bias because of differential death
40 and dropout from the study between the intervention and control groups, the assessments at the
41 various follow-up times were weighted by the inverse of an estimate of the probability of staying in
42 the study, a method explained in the seminal paper by Dufoil et al.²⁵ These probabilities were
43 estimated from the data in logistic regression models for death and dropout with the dyads'
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4 characteristics and the observed primary outcomes from previous visits as covariates. Only the
5 expected scores and inferences for the 36-month follow-up were reported. Differences in mortality
6 and nursing home placement rates between the two groups were evaluated by a hazard ratio (HR)
7 from a Cox regression model. All analyses were done using the intention-to-treat principle.
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10 11 12 **RESULTS**

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15 558 patients were screened for eligibility and 330 patient-caregiver dyads were
16 included: 163 were randomized to DAISY intervention group and 167 to control group (Figure 1).
17 Their demographics, clinical characteristics, and outcome measures at baseline are provided in
18 Table 1. Most patients received cognition enhancing medications (93.3 % cholinesterase inhibitor
19 and 1% NMDA receptor antagonist).¹¹ Overall, the participation rate in the DAISY intervention
20 group was high.¹¹
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29 At 36 months, a total of 130 patients (67 in the intervention group and 63 in the
30 control group) were lost to follow up (Figure 1). In all, 56 patients had deceased, 36 from the
31 DAISY intervention group and 20 from the control group (Figure 1). Patients in the DAISY
32 intervention had a higher mortality rate (HR 1.99; 95% CI: 1.15 to 3.43; P = 0.01). Regarding
33 nursing home placement, 43 patients from DAISY intervention group and 48 from the control group
34 were placed in nursing homes at 36-month follow-up. Data on nursing home placement was missing
35 for five participants in the intervention group. There was no difference between the rates of nursing
36 home placement for the intervention and control groups (HR 0.97; 95% CI: 0.64 to 1.47; P = 0.89).
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47 As reported previously, the 12-month follow-up study observed positive effects of
48 DAISY intervention on preventing the emergence of depressive symptoms (Cornell depression
49 scale, primary patient outcome) and maintaining quality of life (proxy-rated QoL-AD, secondary
50 patient outcome).¹¹ The effect size of DAISY intervention regarding Cornell depression score was -
51 1.58 (-2.79 to -0.37, P = 0.0103) and regarding proxy-rated QoL-AD was 2.14 (0.83 to 3.45; P =
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0.0013). In this 36-month follow-up study, which took place after the DAISY interventions had stopped for two years, there was no significant difference between intervention and control groups regarding these two outcomes (Cornell depression score, $P = 0.93$; proxy-rated QoL-AD, $P = 0.82$; Tables 2 and 3). The effect size of DAISY intervention regarding Cornell depression score was -0.06 (-1.43 to 1.32 ; $P = 0.93$) and regarding proxy-rated QoL-AD was -0.19 (-1.75 to 1.38 , $P = 0.82$). Furthermore, the 36-month follow-up study did not find any long-term effect of DAISY intervention on any of the other primary and secondary outcomes (Tables 2 and 3).

At baseline, the patients were at the very early stage of dementia with a mean MMSE of 24.1 (SD 2.6). At 36-month follow-up, there was a marked fall in MMSE mean scores of 6-7 in both groups, accompanied by a marked deterioration in the patients' quality of life (Table 2). Additionally, the patients were well-functioning in their ADL and had very few behavioural problems at baseline. At 36-month follow-up, ADL had deteriorated markedly and behavioural symptoms had emerged (Table 2). Participants in both group had few depressive symptoms at baseline and minimal changes in mean Cornell Depression Scale scores at 36-month follow-up compared to baseline (Table 2 and 3).

The study found no effect of DAISY intervention on caregivers' self-rated quality of life and depressive symptoms at 36-month follow-ups. The caregivers were characterized by lack of depressive symptoms and a high self-rated quality of life at baseline (Table 1). At 36-month follow-up, their depressive symptoms and self-rated quality of life had changed minimally from baseline (Table 2 and 3).

DISCUSSION

This study did not find any long-term effect of an intensive psychosocial intervention (DAISY intervention) on patients and caregivers beyond the effect of structured follow-up support.

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4 To our knowledge, this study is the largest randomised controlled trial of early
5 psychosocial intervention for patients with mild Alzheimer' disease and their caregivers to date,
6 with a long follow-up of three years. It is a study of solid methodology, strictly adhering to
7 CONSORT recommendations. A-priori sample size calculation was done. The measures for
8 primary and secondary outcomes are reliable scales, which are commonly used in routine clinical
9 practice and in intervention studies across cultures.^{26,27} Proper randomisation, allocation
10 concealment, rater-blinded evaluation of outcomes, and adjustment for multiple testing were
11 rigorously carried out to reduce biases that could lead to type I errors.¹¹ The multicomponent semi-
12 tailored intervention programme was intensive in both content and duration, targeted multiple
13 needs, tended to the individual needs, and simultaneously involved caregivers and patients; thus
14 having the characteristics that defined successful intervention programs documented in the
15 literature.^{2,5,7} Since ours was one of the first studies to examine the effect of support and counselling
16 programmes in patients with very mild dementia, no previous consensus exists concerning gold
17 standards for assessing efficacy. Therefore, multiple primary and secondary outcomes were
18 exploratively chosen based on the specific aims of the DAISY intervention and on the outcomes
19 from similar intervention studies for patients with more advanced dementia.¹ Consequently, to
20 avoid finding spurious effects, a significance level was set at $P = 0.0005$, which was subsequently
21 criticized for being too conservative.¹² All patients in this study had primary caregivers who were
22 very involved in caregiving, a situation that cannot be generalised to all patients with dementia in
23 Denmark.

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49 Although not statistically significant for this adjusted P value, DAISY intervention
50 did produce small positive effects on reducing depressive symptoms and maintaining quality of
51 life for the patients at 12-month follow-up.¹¹ The effect size of DAISY intervention regarding
52 Cornell depression score was -1.58 (-2.79 to -0.37 , $P = 0.0103$) and regarding proxy-rated QoL-AD
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4 was 2.14 (0.83 to 3.45; $P = 0.0013$). The disease-specific QoL-AD is probably more sensitive to
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6 measure the effect of psychological interventions than general EQ-VAS.²⁷ At 36-month follow-up,
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8 these positive effects were no longer present. Between 12- and 36-month follow-up, there was
9
10 significant decline in patients' cognition, quality of life, and ADL. During this time period, there
11
12 was no continuing intervention or support. Initially, the study was intended to end at 12-month
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14 follow-up. However, we received additional funding to carry out follow-up at 36 months. The
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16 timing and duration of DAISY intervention could have missed a period of significant decline when
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18 intervention could have been more beneficial. Possibly, the positive trends observed at the 12-
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20 month follow-up could have been maintained or enhanced had the intervention continued an
21
22 additional two years. Evidence from the very limited literature seems to support the hypothesis that
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24 the positive effects of psychosocial interventions could be lost without continuous reinforcement.
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26 There are few randomised controlled trials assessing the efficacy of psychosocial intervention that
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28 specifically targets community-dwelling patients with dementia.^{6,10} Most trials had short follow-up
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30 period, usually three to six months. One trial showed that a three-month programme of intensive
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32 physical exercise for the patients combined with teaching caregivers strategies to manage patients'
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34 behavioural problems improved the patients' physical functioning and depressive symptoms.²⁸ At
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36 24-month follow-up, the improvement in physical functioning was still significant, but the
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38 improvement of depressive symptoms was no longer present.²⁸ In contrast, another trial with eight-
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40 year follow-up reported delayed nursing home placement for patients by providing a
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42 multicomponent interventions for the caregivers and patients; the ten-day intervention program was
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44 followed by continuous support over the telephone weekly for the first year and yearly thereafter for
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46 the next seven years.²⁹

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53 In our study, there are some possible explanations for the non-significant positive
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55 effects found at 12-month concerning patients' depressive symptoms and quality of life and the
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4 disappearance of these effects at 36-month follow-up. First, it could be a floor effect. Our patients
5 had minimal depressive symptoms and relatively high scores of QoL-AD at baseline. A randomised
6 controlled trial using support group intervention for community-dwelling patients with mild
7 Alzheimer's disease and their caregivers showed that patients who experienced improvement in
8 their depressive symptoms had significantly more depressive symptoms at baseline and higher level
9 of distress.³⁰ Second, there was no need assessment at baseline. Probably, participants with more
10 symptoms and at greater need should have received the full intensive intervention programme and
11 regular support follow-up was sufficient for those who had minimal symptoms and needs at
12 baseline. Third, the control group also received some intervention that is much better than the usual
13 practice in Denmark.³¹ They had regular follow-ups when they could speak about emerging
14 psychosocial and health problems, receive information about available resources, and get referred to
15 relevant health professionals if needed. It is noteworthy that despite the marked decline in patients'
16 global cognitive function, quality of life, and ADL between 12- and 36-month follow-ups,
17 participants in both group had minimal changes in mean Cornell Depression Scale scores compared
18 to baseline. This could be an indication that the regular follow-ups offered in this study were
19 sufficient enough to produce a long-term effect in preventing the conversion into clinical depression
20 for the patients. Fourth, as mentioned above, the intervention should probably continue
21 longitudinally following the clinical progression in these patients to show long-term positive
22 effects. The study did not find any long-term effect on DAISY intervention on the caregiver
23 outcomes. Previous studies have shown positive responses to interventions from caregivers with
24 high levels of depression and anxiety at baseline.¹⁰ For this mostly asymptomatic group of
25 caregivers in our study, perhaps follow-up at regular intervals provided enough information and
26 support to prevent the emergence of depressive symptoms and maintain good life quality.
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4 It is not known why patients in the intervention group had higher mortality than those
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6 in the control group. This increased mortality was unlikely to be caused by the intervention, as the
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8 nature of the intervention program did not subject the patients to any health risk. Using the data
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10 from Statistics Denmark (www.dst.dk), the incidence of death for the age-matched general
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12 population over the same time period was found to be similar to that of the DAISY intervention
13
14 group. The control group however had lower incidence of death compared to the general
15
16 population. At baseline, the quality of life of the patients in the intervention group was rated as
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18 poorer than that of the control group, both by the patients themselves and by their caregivers (Table
19
20 1). Although not statistically significant, there were small socioeconomic and clinical differences
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22 that could be responsible for the higher mortality rate in the intervention groups. More patients in
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24 the intervention group lived alone (4% difference), rented their house (7% difference), had more co-
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26 morbidities (4.4% difference), and were diagnosed with mixed AD and vascular dementia (4.2%
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28 difference, Table 1). Whether these differences could contribute to the higher mortality in the
29
30 intervention group is uncertain. It is known that older people living alone have higher mortality than
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32 those living with others.³² Currently, there is insufficient evidence in the literature concerning the
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34 effect of psychosocial intervention on patient mortality, as studies looking at this effect are
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36 scarce.^{5,33}

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42 The same patient characteristics in the DAISY intervention group stated above could
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44 also explain the lack of effect concerning nursing home placement.³⁴ Additionally, continuous
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46 intervention and follow-up between 12 and 36 months could have been needed to produce a positive
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48 long-term effect on nursing home placement. Randomised controlled trials that reported positive
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50 long-term effect of psychosocial intervention on patients' nursing home placement provided
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52 continuous support and counselling over the phone for eight-nine years.^{29,35} In contrast, intervention
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4 lasting two years but without continuous follow-up and support showed no long-term effect on
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6 nursing home placement.³³
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9 Although this study found no long-term effect of DAISY intervention, a qualitative
10 study linked to this randomised controlled trial showed that 80% of patients and 94% of caregivers
11 in the intervention group found the intervention overall beneficial. Patients felt that their self-esteem
12 was improved and they could better manage their daily life and social relations. Caregivers felt that
13 they were more confident and competent to cope with the challenges of caring for relatives with
14 AD. After the intervention, both patients and caregivers looked for support groups to join
15 permanently and caregivers sought continuing counseling.³⁶ In contrast to randomised clinical trials
16 about pharmacological interventions, we did not carry out the DAISY study to justify the reason for
17 providing psychosocial intervention for patients with dementia and their caregivers, whose needs
18 for information, counselling, and support cannot be denied. What we can conclude from this study
19 is that since we could not show positive effects in the quantitative analyses, we should not offer
20 psychosocial intervention indiscriminately to all patients with very mild dementia and their
21 caregivers, but we should probably assess their needs and offer intervention only to those who need.
22 Regular follow-up is therefore important to identify the arising needs that require intervention.
23 Probably, the type, dose and intensity, and duration of early intervention should be more tailored to
24 match the needs of patients and their caregivers at baseline to maximize benefit, economize
25 resources, and avoid unnecessary intervention burden. The intervention program should perhaps be
26 designed so that patients and caregivers with greater needs at baseline receive more intensive
27 interventions that cater to their specific needs, those with lesser needs receive a basic intervention
28 program of lower intensity, and those with minimal or no needs receive no intervention at all. To
29 obtain long-term effect, early intervention should probably have a longitudinal and fluid course that
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4 follows the disease progression, being continuously modified according to the needs that arise.
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6 These are the questions to be answered in future studies.
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8
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4 submitted work in the previous three years; no other relationships or activities that could influence
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6 the submitted work.
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22 **Contributorship Statement**

23 KP drafted the manuscript. FBW, VS, NK, MLHR, and GW outlined the statistical analysis. VS
24 conducted the statistical analysis in consultation with NK. FBW, AE, DVB, AV and GW designed
25 and conducted the DAISY study. KP, FBW, and GW worked with interpretation of data analysis.
26 All authors assisted in editing this manuscript. All authors read and approved the final manuscript.
27 All authors are guarantors for the scientific integrity of the articles.
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30 **Data sharing**

31 The dataset is available upon request to Gunhild Waldemar (Gunhild.waldemar@rh.regionh.dk)
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6 **Figure 1: Trial flow for Danish Alzheimer Intervention Study (DAISY)**
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8 ¹ Patients and caregivers. ² Full compliance is defined as participation from both the caregiver and
9 the patient in at least 3 courses and 3 counselling sessions each. ³ In the analysis accounting for drop
10 outs, information from all participating dyads were incorporated.
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For peer review only

Table 1: Baseline characteristics of patients with Alzheimer's disease and their caregivers who participated in the Danish Alzheimer Intervention Study (DAISY). Values are numbers (percentages) of participants unless stated otherwise

Patients' characteristics	Intervention (n=163)	Control (n=167)
Sex		
Male	76 (46.6)	75 (44.9)
Female	87 (53.4)	92 (55.1)
Mean (SD) age (years)	76.5 (7.7)	75.9 (6.6)
Household status		
Living alone	54 (33.1)	48 (28.7)
Living with others	109 (66.9)	119 (71.3)
Home		
Rented	66 (40.5)	56 (33.5)
Owned	97 (59.5)	111 (66.5)
Education		
None	60 (36.8)	57 (34.1)
< 3 years	39 (23.9)	49 (29.3)
≥ 3 years	64 (39.3)	61 (36.5)
Charlson comorbidity index		
No comorbidity	64 (39.3)	73 (43.7)
One comorbidity	75 (46.0)	65 (38.9)
≥ 2 comorbidities	24 (14.7)	29 (17.4)
Diagnosis		
Pure Alzheimer's disease	112 (68.7)	127 (76.1)
Mixed Alzheimer's disease and vascular dementia	44 (27.0)	38 (22.8)
Lewy body dementia	7 (4.3)	2 (1.2)
Caregiver' characteristics		
Sex		
Male	54 (33.1)	56 (33.5)
Female	109 (66.9)	111 (66.5)
Mean (SD) age (years)	65.5 (12.7)	66.5 (12.7)
Relation		
Spouse	104 (63.8)	111 (66.5)
Child or child in law	45(27.6)	41(24.5)
Other	14 (8.6)	15 (9.0)
Living with patient		
Yes	101/162 (62.4)	112/166 (67.5)
No	61/162 (37.6)	54/166 (32.5)
Home		
Rent	45 (27.6)	45 (26.9)
Own	118 (72.4)	122 (73.1)
Education		

None	41 (25.2)	37/166 (22.3)
< 3 years	46 (28.2)	63/166 (37.9)
≥ 3 years	76 (46.6)	66 /166 (39.8)
Outcome measures at baseline		
Primary patient outcomes		
Mean (SD) MMSE	24.0 (2.5)	24.1 (2.7)
Mean (SD) Cornell Depression Scale	5.2 (4.8)	4.4 (4.0)
Mean (SD) proxy-rated EQ-VAS	62.1 (18.4) (n=162)	64.7 (20.4)
Primary caregiver outcome		
Mean (SD) EQ-VAS	79.3 (16.3) (n=162)	81.4 (16.3)
Mean (SD) GDS	4.74 (5.2) (n=162)	4.71 (5.0)
Secondary patient outcome		
Mean (SD) QoL-AD (proxy-rated)	33.0 (6.1)	34.7 (6.6)
Mean (SD) NPI-Q	3.9 (3.6)	3.9 (3.7)
Mean (SD) ADSC-ADL	61.2 (11.4)	61.8 (11.4)

MMSE: Mini Mental State Examination. EQ-VAS: European Quality of Life Visual Analogue Scale. GDS: Geriatric Depression Scale. QoL-AD: Quality of Life Scale for Alzheimer's Disease. NPI-Q: Neuropsychiatric Inventory Questionnaire. ADSC-ADL: Alzheimer's Disease Cooperative Study Activities of Daily Living Scale.

Table 2: Outcome measures of DAISY psychosocial interventions based on completed response at 36-month follow-up. Values are means (SD) unless stated otherwise.

	Observed scores		Changes from baseline	
	Intervention	Control	Intervention	Control
Primary patient outcomes				
MMSE	17.8 (6.7) (n=84)	17.9 (7.1) (n=94)	-6.21 (6.17) (n=84)	-6.35 (6.26) (n=94)
Cornell Depression Scale	5.57 (4.78) (n=93)	5.17 (4.19) (n=101)	1.29 (4.94) (n=93)	0.74 (4.45) (n=101)
Proxy-rated EQ-VAS	50.7 (20.3) (n=95)	52.3 (21.0) (n=102)	-12.88 (20.3) (n=95)	-12.46 (19.0) (n=102)
Primary caregiver outcomes				
EQ-VAS	79.4 (16.1) (n=94)	79.0 (18.0) (n=103)	-0.79 (16.5) (n=94)	-1.49 (16.5) (n=103)
GDS	5.26 (5.43) (n=94)	4.51 (5.26) (n=103)	0.81 (4.83) (n=94)	0.14 (4.52) (n=103)
Secondary patient outcomes				
QoL-AD (proxy-rated)	30.5 (5.1) (n=96)	32.1 (6.2) (n=103)	-2.89 (4.89) (n=96)	-2.84 (-2.00) (n=103)
NPI-Q	5.21 (4.43) (n=96)	5.05 (4.80) (n=104)	1.57 (4.43) (n=96)	1.20 (4.68) (n=104)
ADSC-ADL	35.3 (19.4) (n=96)	41.3 (20.8) (n=104)	-26.7 (16.6) (n=96)	-22.3 (19.6) (n=104)

MMSE: Mini Mental State Examination. EQ-VAS: European Quality of Life Visual Analogue Scale. GDS: Geriatric Depression Scale. QoL-AD: Quality of Life Scale for Alzheimer's Disease. NPI-Q: Neuropsychiatric Inventory Questionnaire. ADSC-ADL: Alzheimer's Disease Cooperative Study Activities of Daily Living Scale.

Table 3: Outcomes of DAISY psychosocial interventions based on inverse probability weighting of respondents with non-missing data at 36-month follow up (intention to treat analyses adjusted for attrition). Values are means* (95% CI) unless stated otherwise.

	Estimated endpoint scores			Mean change from baseline		
	Intervention	Control	P value of t test	Intervention	Control	P value of t test
Primary patient outcomes:						
MMSE	18.0 (16.5 to 19.6)	18.1 (16.4 to 19.8)	0.96	-6.57 (-7.89 to -5.25)	-6.56 (-7.98 to -5.14)	0.99
Cornell Depression Scale	4.89 (3.75 to 6.03)	4.20 (3.10 to 5.31)	0.32	0.59 (-0.49 to 1.66)	0.64 (-0.21 to 1.49)	0.93
Proxy-rated EQ-VAS	55.9 (51.0 to 60.8)	60.1 (54.6 to 65.6)	0.20	-12.44 (-16.64 to -8.24)	-10.77 (-15.19 to -6.35)	0.59
Primary caregiver outcome						
EQ-VAS	80.3 (76.2 to 84.3)	79.5 (74.5 to 84.6)	0.78	0.14 (-3.18 to 3.47)	-2.71 (-6.66 to 1.23)	0.28
GDS	5.83 (4.27 to 7.38)	4.98 (3.43 to 6.53)	0.29	0.47 (-0.58 to 1.52)	-0.33 (-1.39 to 0.72)	0.29
Secondary patient outcome						
QoL-AD (proxy-rated)	31.0 (29.3 to 32.6)	32.8 (31.2 to 35.3)	0.03	-2.83 (-3.85 to -1.80)	-2.64 (-3.82 to -1.46)	0.82
NPI-Q	4.90 (3.85 to 5.96)	4.73 (3.53 to 5.93)	0.79	1.48 (0.55 to 2.40)	1.30 (0.37 to 2.23)	0.80
ADSC-ADL	34.1 (29.1 to 39.2)	39.9 (35.1 to 44.7)	0.05	-26.9 (-30.8 to -22.9)	-21.7 (-25.6 to -17.7)	0.07

MMSE: Mini Mental State Examination. EQ-VAS: European Quality of Life Visual Analogue Scale. GDS: Geriatric Depression Scale. QoL-AD: Quality of Life Scale for Alzheimer's Disease. NPI-Q: Neuropsychiatric Inventory Questionnaire. ADSC-ADL: Alzheimer's Disease Cooperative Study Activities of Daily Living Scale.

*Means are estimated from a longitudinal model where selective dropout is accounted for by inverse probability weighting; the inclusion of a categorical indicator variable for treating centre accounts for possible clustering within centre; confidence intervals and P values are calculated with generalised estimating equations.

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8 **Three-year follow-up on the efficacy of psychosocial interventions for patients with mild**

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10 **dementia and their caregivers: the multicentre, rater blinded, randomised Danish Alzheimer**

11 **Intervention Study (DAISY)**

12 Phung K¹, Waldorff FB^{1,2}, Buss DV¹, Eckermann A¹, Keiding N³, Rishøj S¹, Siersma V², Sørensen
13 J⁴, Søgaard R⁴, Sørensen LV¹, Vogel A¹, Waldemar G¹

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25 Trial registration: The study was registered in the Clinical Trial Database ([www.controlled-](http://www.controlled-trials.com/ISRCTN74848736)
26 [trials.com/ISRCTN74848736](http://www.controlled-trials.com/ISRCTN74848736)).

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Abstract

Objectives: To examine the long-term efficacy at 36-month follow-up of an early psychosocial counselling and support programme lasting 8-12 months for community-dwelling patients with mild Alzheimer's disease and their caregivers.

Design: Multicentre, randomised, controlled, rater-blinded trial.

Setting: Primary care and memory clinics in five Danish districts.

Participants: 330 home-dwelling patients with mild Alzheimer's disease and their primary caregivers (dyads).

Interventions: Dyads were randomized to receive intervention during the first year after diagnosis.

~~Both intervention and control groups had -and- follow-up visits at 3, 6, 12, and 36 months. in the intervention group or follow up only in the control group.~~

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Main outcome measures: Primary outcomes for the patients assessed at 36-month follow-up were changes from baseline in global cognitive function (Mini Mental State Examination), depressive symptoms (Cornell Depression Scale), and proxy rated EuroQoL quality of life on visual analogue scale. The primary outcomes for the caregivers were changes from baseline in depressive symptoms (Geriatric Depression Scale) and self-rated EuroQoL quality of life on visual analogue scale. The secondary outcome measures for the patient were proxy rated Quality of Life Scale for Alzheimer's Disease (QoL-AD), Neuropsychiatric Inventory-Questionnaire, Alzheimer's Disease Cooperative Study Activities of Daily Living Scale, all-cause mortality, and nursing home placement.

Results: At 36-month follow-up, two years after the completion of the DAISY intervention, the ~~unadjusted~~ positive ~~effects~~ ~~trends~~ previously detected at 12-month follow-up in one patient primary outcome (Cornell depression score) and one patient secondary outcome (proxy-rated QoL-AD) disappeared (Cornell depression score, $P = 0.93$; proxy-rated QoL-AD, $P = 0.81$). No long-term

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8 effect of DAISY intervention on any other primary and secondary outcomes at 36-month follow-up
9 was found.

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11 Conclusions: ~~For patients with very mild dementia and low level of distress, initial need assessment~~
12 ~~is of paramount importance to determine whether intervention is necessary and to tailor the~~
13 ~~intervention modalities accordingly. Regular reassessments are needed to modify the interventions~~
14 ~~longitudinally.~~

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16 For patients with very mild Alzheimer's disease and their caregivers, an intensive, multicomponent,
17 semi-tailored psychosocial intervention program with counselling, education, and support during
18 the first year after diagnosis did not show any positive long-term effect on primary and secondary
19 outcomes.

26 Article summary

27 Article focus:

- 28 • Psychosocial intervention for caregivers of patients with Alzheimer's disease has been
29 shown to have beneficial effects on patients' and caregivers' psychological morbidity.
30 Results are inconsistent concerning nursing home placement of the patients. Studies with
31 psychosocial intervention for both patients and caregivers are scarce. Few have targeted
32 patients with very mild Alzheimer's disease. In general, there is a lack of long-term follow
33 up beyond 12 months.
- 34 • It was hypothesized that the DAISY (Danish Alzheimer Intervention Study) interventions, a
35 multifaceted and semi-tailored intervention programme offered to patients with AD and
36 their primary caregivers during the first year after the diagnosis, could have a long-term
37 effect in preventing the emergence of depressive symptoms, improving quality of life for the
38 patients and the caregivers, stabilising the patients' cognitive function, and delaying nursing
39 home placement

Key messages

- An intensive, multicomponent, semi-tailored psychosocial intervention program with counselling, education, and support to patients with very mild Alzheimer's disease and their caregivers during the first year after diagnosis did not improve the three-year outcomes concerning patients' and caregivers' psychological morbidity and patients' nursing home placement compared to structured and systematic follow-up support.
- To maximize benefit, economize resources, and avoid unnecessary intervention burden, the needs of patients with very mild dementia their caregivers should probably be assessed to determine whether psychosocial intervention is necessary and tailor the intervention modalities accordingly. Regular reassessments probably are needed to identify emerging needs and modify the interventions longitudinally.

Strengths and limitations

- This is the largest randomised controlled trial of early psychosocial intervention for patients with mild Alzheimer' disease and their caregivers to date, with a long follow-up of three years.
- It is a study of solid methodology, strictly adhering to CONSORT recommendations.
- The multicomponent semi-tailored intervention programme was intensive in both content and duration, targeted multiple needs, tended to the individual needs, and simultaneously involved caregivers and patients; thus having the characteristics that defined successful intervention programs documented in the literature.
- Multiple primary and secondary outcomes were chosen based on the specific aims of the DAISY intervention and on the outcomes from similar intervention studies for patients with

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8 more advanced dementia. To avoid finding spurious effects, a conservative significance
9 level was set at $P = 0.0005$.

- 10 • All patients had primary caregivers who are very involved in caregiving, a situation that
11 cannot be generalised to all patients with dementia in Denmark.
- 12 • There was no need assessment at baseline.
- 13 • Intervention lasted one year but without continuous follow-up and support during the
14 subsequent two years.

21 22 23 INTRODUCTION

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26 Psychosocial interventions for patients with Alzheimer's disease (AD) and their
27 caregivers have gained recognition during the last two decades. The majority of patients with
28 dementia live in their own homes with their caregivers, usually their spouses, who bear the
29 responsibly of caregiving.¹ Caring for family members with dementia has long been considered as
30 the most stressful type of family caregiving, predisposing caregivers to mental and physical
31 illnesses and increasing their risk for death.² Previously an under-researched area, the needs of
32 patients with AD have received more attention in recent years, with studies documenting their needs
33 for information about their illness, for help to cope with their disabilities, for social recognition and
34 support, and for a decent quality of life with meaningful social contact and activities.³ Patients'
35 unmet needs can result in mood and behavioural problems, safety issues, social isolation, and
36 increased risk for nursing home placement and death.⁴ Meta-analyses and systematic reviews of the
37 numerous clinical trials assessing the efficacy of psychosocial interventions for caregivers have
38 shown a significant effect of interventions on reducing caregivers' psychological morbidity and
39 reduce patients' neuropsychiatric symptoms.^{5,6,7,8,9} Studies examining the effect of psychosocial
40 intervention on patients' mortality and nursing home placement are scarce and the results are
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8 inconsistent.^{5,10} Studies that included psychosocial interventions for the patients are limited,
9 providing anecdotal evidence for positive effects of interventions on patients' cognitive function,
10 psychological morbidity, and time to nursing home placement.¹⁰ Today, thanks to the remarkable
11 advances in diagnosing dementia, patients can be diagnosed at an early stage when their relatively
12 intact autonomy and insight enable them to convey their needs and actively participate in
13 intervention programmes. The rapidly growing number of people with AD in the coming years, a
14 considerable proportion of them diagnosed in the early stages, presents a pressing need to develop
15 and validate intervention programmes that focus on the needs of patients with mild dementia and
16 their caregiver and involve both parties in the intervention.
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25 It was hypothesized that the DAISY (Danish Alzheimer Intervention Study)
26 interventions, a multifaceted and semi-tailored intervention programme offered to patients with AD
27 and their primary caregivers during the first year after the diagnosis, could have a long-term effect
28 in preventing the emergence of depressive symptoms, improving quality of life for the patients and
29 the caregivers, stabilising the patients' cognitive function, and delaying nursing home placement.¹
30 The results of the 12-month follow-up were published in BMJ in 2012, showing no significant
31 difference in outcomes between the DAISY intervention and the control groups.¹¹ However, the
32 significant level corrected for multiple testing (P=0.0005) was subsequently criticized for being too
33 conservative, given that an alternative correction method could have given another conclusion.¹²
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42 ~~Before adjustment for multiple testing was carried out, the data analysis of the results a~~At 12-month
43 follow-up, ~~had shown there were indeed statistical significance in positive trends in~~ one primary
44 patient outcome (Cornell depression Scale score, P = 0.0103) and one secondary patient outcome
45 (proxy-rated quality of life QoL-AD, P = 0.0013) in favour of the DAISY intervention group.¹¹
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50 Therefore, a 36-month follow-up was subsequently carried out to follow the evolution of these
51 ~~positive trends outcomes~~. This paper reports on the results of this follow-up.
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METHODS

Detailed description of the study rationale, methods, design, randomisation, and sample size has been published.¹

Trial Design

DAISY was a large multicentre, rater blinded, one-year randomised controlled trial of the efficacy of intensive psychosocial intervention for patients with mild AD and their caregivers. It was an exploratory randomised clinical trial with multiple primary and secondary outcomes.

Participants

The patients were recruited from five Danish districts. One designated memory clinic in each district recruited the patients for the trial. Each recruiting centre had one study coordinator and one physician who assessed the patients for eligibility. Patients were referred from local memory clinics as well as private practice in psychiatry, neurology, geriatrics and family medicine. If referred from private practice, dementia diagnosis was confirmed by specialists in the recruiting memory clinic.

The inclusion criteria were: 1) Home living patients diagnosed within the past 12 months with AD, mixed AD with vascular component, or Lewy body dementia, 2) 50 years of age or older, 3) Mini Mental State Examination (MMSE) score ≥ 20 ,¹³ and 4) having one participating primary caregiver. The primary caregiver was defined as the main person responsible for the informal care of the patient with minimum weekly contact. All patients met DSM-IV criteria for dementia,¹⁴ NINCDS-ADRDA criteria for probable Alzheimer's disease,¹⁵ or McKeith criteria for Lewy Body dementia.¹⁶ Patients with mixed Alzheimer's disease were those with probable Alzheimer's disease and minor vascular changes on cranial CT that could contribute to their symptoms.

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8 Patients with severe somatic or psychiatric co-morbidities (including impaired hearing
9 or vision) that would significantly impair their compliance with the DAISY intervention programme
10 were excluded. Patients who had already been involved in other intervention programmes were also
11 excluded. Patient-caregiver dyads were randomised to the DAISY intervention group, in which they
12 were provided with intensive psychosocial interventions and follow-up support at 3, 6, and 12
13 months; or to the control group, in which they were only provided with follow-up support at 3, 6,
14 and 12 months. The study was subsequently extended and the patients and their caregivers were
15 asked to give a separate consent to an additional follow-up at 36 months.
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23 *Intervention*

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25 A multifaceted and semi-tailored psychosocial intervention programme, described in
26 details in our previous reports,^{1,11} was designed to provide counselling, information, and support to
27 patients with mild dementia and their caregivers in the intervention group. The study coordinator in
28 each centre, an experienced nurse specialising in caring for patients with dementia and having
29 received special training in counselling for the study (constructivist approach),¹⁷ implemented the
30 intervention within the first month after inclusion in the trial. Consisting of five key components,
31 the intervention focused on positive resources, intact function, retained skills, and feasible activities
32 for the patients: 1) The study coordinator provided seven individual counselling sessions tailored to
33 the needs of the patients and their caregivers: two for the patient alone, two for the caregiver alone,
34 two for the patient-caregiver dyad, and one with the dyad together with their family network
35 (optional); 2) The study coordinator provided outreach telephone counselling 5-8 times with 3-4
36 week intervals to maintain regular contact and follow up on the individual counselling sessions; 3)
37 Using log books, the patients and their caregivers independently kept track of the thoughts and daily
38 issues that they wanted to discuss at the counselling sessions; 4) Experts in the field of dementia
39 were invited to teach five standard courses as group intervention with separate courses for patients
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8 and caregivers to provide general information about dementia and forum for discussion, sharing
9 information, and support; 5) Patients and caregivers were provided with information folders
10 produced especially for the purpose of the study about dementia causes, diagnosis and treatment,
11 legal issues, and resources for social support. The intervention program lasted 8 to 12 months. Full
12 compliance was defined as adherence with the major components of the intervention program:
13 Patients who participated with their caregivers in at least 3 counselling sessions (not including the
14 optional network session) and in at least 3 teaching course sessions.

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21 The patients in both the intervention and the control groups were followed up at 3, 6,
22 12, and 36 months. ~~when they were inquired about their symptoms and daily activities and
23 informed about available support programmes in their local communities, which they could freely
24 take part in. Furthermore, health care needs were identified and participants were referred to local
25 health professionals if necessary. Attempts were made to provide similar treatment for both
26 intervention and control participants in all respects other than the add-on DAISY intervention. At
27 each follow-up visit, participants in both groups were interviewed about their current symptoms and
28 daily life issues, and informed about available support program (if any) in their local communities.
29 Both groups were free to participate in such support programs during the study and participation in
30 these support activities was registered for both groups. Identified special needs led to referral to
31 local care facilities when available and relevant.~~

32 33 34 35 36 37 38 39 40 41 42 *Outcomes*

43 44 Primary outcomes for the patients:

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46 1. Global cognitive function: The patient's global cognitive function was assessed using Mini
47 Mental State Examination (MMSE).¹³ The sum of scores ranges from 0 to 30. Higher scores
48 indicate better cognitive function.
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2. Depressive symptoms: Cornell Scale for Depression in Dementia was used to assess the patient's depressive symptoms through an interview with both the patient and caregiver.¹⁸ The scale has 19 items, each item rating a specific depressive symptom in increasing severity (0-2), yielding a total score ranging from 0 to 38, with higher scores indicating more depressive symptoms. A score ≥ 8 indicates significant depressive symptoms and a score ≥ 10 indicates major depression.
3. Proxy rated quality of life: The primary caregiver evaluated the patient's health-related quality of life using the EuroQoL EQ-5D,¹⁹ a questionnaire inquiring about mobility, self-care, activities, pain, discomfort, anxiety, and depression. Quality of life was rated using a Visual Analogue Scale (EQ-VAS) with scores ranging from 0 to 100 with higher scores signifying better quality of life.

Primary outcomes for the primary caregivers

1. Depressive symptoms: The caregivers rated their own depressive symptoms using the Geriatric Depression Scale (GDS).²⁰ The total score ranges from 0 to 30 with higher score indicating more depressive symptoms. A cut-off score of 10 distinguishes between depressed and non-depressed individuals.
2. Self-rated quality of life: The caregivers rated their own health-related quality of life using the EQ-VAS.¹⁹ The scores range from 0 to 100 with high scores indicating good quality of life.

Secondary outcomes for the patients

1. Proxy-rated quality of life, AD-specific: The caregiver rated the patient's quality of life using Quality of Life Scale for Alzheimer's Disease (QoL-AD),²¹ a 13-item scale measuring disease-specific quality of life in people with AD. Total score ranges from 13 to 52 with higher scores indicating better quality of life.

2. Neuropsychiatric symptoms: The patient's neuropsychiatric and behavioural symptoms were assessed through an interview with the caregiver using Neuropsychiatric Inventory-Questionnaire (NPI-Q).²² Total score ranges from 0 to 36 with higher scores indicating more severe disturbances.
3. Activities of daily living: The caregiver completed the Alzheimer's Disease Cooperative Study Activities of Daily Living Scales for clinical trials in Alzheimer's disease (ADCS-ADL)²³ to assess the patient's activities of daily living. ADCS-ADL is a 23-item scale with total scores ranging from 0 to 78. Higher scores indicating better functioning.
4. Mortality and nursing home placement: The Danish Civil Registration System²⁴ was used together with personal contacts with the caregivers to collect information regarding death and nursing home placement. In case of doubt, the local district authority or the residential place was contacted to check if the address was registered as a nursing home.

Baseline and follow-up assessments

Both patients and their caregivers were invited to participate in all the assessments. The local study coordinator carried out the baseline assessment prior to randomisation at the local study centre. Independent raters blind to group assignment carried out 6-, 12- and 36-month follow-up assessments during home visits. The raters were neither involved in the intervention program nor employed in the same institutions as the study coordinators. The efficiency of concealment was checked through questionnaires administered to the raters at the end of each follow-up visit. None of the raters visited the same patient-caregiver dyad more than once.

Statistical methods

Characteristics and outcome measures at baseline of the dyads in the intervention and control groups were compared using Student's t-tests for continuous variables and χ^2 tests for categorical variables. With linear models on the full data of up to four observations per dyad, we

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8 compared the difference in development of the primary and secondary outcomes between
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10 randomisation groups during the follow-up period, using generalised estimating equations to
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12 account for repeated measurements; the inclusion of a categorical centre indicator variable account
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14 for possible clustering by treating centre. To adjust for possible bias because of differential death
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16 and dropout from the study between the intervention and control groups, the assessments at the
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18 various follow-up times were weighted by the inverse of an estimate of the probability of staying in
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20 the study, [a method explained in the seminal paper by Dufoil et al.](#)²⁵ These probabilities were
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22 estimated from the data in logistic regression models for death and dropout with the dyads'
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24 characteristics and the observed primary outcomes from previous visits as covariates. Only the
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26 expected scores and inferences for the 36-month follow-up were reported. Differences in mortality
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28 and nursing home placement rates between the two groups were evaluated by a hazard ratio (HR)
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30 from a Cox regression model. All analyses were done using the intention-to-treat principle.

31 RESULTS

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33 558 patients were screened for eligibility and 330 patient-caregiver dyads were
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35 included: 163 were randomized to DAISY intervention group and 167 to control group (Figure 1).
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37 Their demographics, clinical characteristics, and outcome measures at baseline are provided in
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39 Table 1. Most patients received cognition enhancing medications (93.3 % cholinesterase inhibitor
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41 and 1% NMDA receptor antagonist).¹ Overall, the participation rate in the DAISY intervention
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43 group was high.¹¹

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45 At 36 months, a total of 130 patients (67 in the intervention group and 63 in the
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47 control group) were lost to follow up (Figure 1). In all, 56 patients had deceased, 36 from the
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49 DAISY intervention group and 20 from the control group (Figure 1). Patients in the DAISY
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51 intervention had a higher mortality rate (HR 1.99; 95% CI: 1.15 to 3.43; P = 0.01). Regarding
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53 nursing home placement, 43 patients from DAISY intervention group and 48 from the control group

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8 were placed in nursing homes at 36-month follow-up. Data on nursing home placement was missing
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10 for five participants in the intervention group. There was no difference between the rates of nursing
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12 home placement for the intervention and control groups (HR 0.97; 95% CI: 0.64 to 1.47; P = 0.89).

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14 As reported previously, the 12-month follow-up study observed positive ~~trends-effects~~
15 ~~concerning the effect~~ of DAISY intervention on preventing the emergence of depressive symptoms
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17 (Cornell depression scale, primary patient outcome) and maintaining quality of life (proxy-rated
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19 QoL-AD, secondary patient outcome).¹¹ The effect size of DAISY intervention regarding Cornell
20 depression score was -1.58 (-2.79 to -0.37, P = 0.0103) and regarding proxy-rated QoL-AD was
21 2.14 (0.83 to 3.45; P = 0.0013). In this 36-month follow-up study, which took place after the
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23 DAISY interventions had stopped for two years, there was no significant difference ~~in~~ between
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25 intervention and control groups regarding these two outcomes (Cornell depression score, P = 0.93;
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27 proxy-rated QoL-AD, P = 0.82; Tables 2 and 3). The effect size of DAISY intervention regarding
28 Cornell depression score was -0.06 (-1.43 to 1.32; P = 0.93) and regarding proxy-rated QoL-AD
29 was -0.19 (-1.75 to 1.38, P = 0.82). Furthermore, the 36-month follow-up study did not find any
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31 long-term effect of DAISY intervention on any of the other primary and secondary outcomes
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33 (Tables 2 and 3).
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38 At baseline, the patients were at the very early stage of dementia with a mean MMSE
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40 of 24.1 (SD 2.6). At 36-month follow-up, there was a marked fall in MMSE mean scores of 6-7 in
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42 both groups, accompanied by a marked deterioration in the patients' quality of life (Table 2).
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44 Additionally, the patients were well-functioning in their ADL and had very few behavioural
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46 problems at baseline. At 36-month follow-up, ADL had deteriorated markedly and behavioural
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48 symptoms had emerged (Table 2). Participants in both group had few depressive symptoms at
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50 baseline and minimal changes in mean Cornell Depression Scale scores at 36-month follow-up
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52 compared to baseline (Table 2 and 3).
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8 The study found no effect of DAISY intervention on caregivers' self-rated quality of
9 life and depressive symptoms at 36-month follow-ups. The caregivers were characterized by lack of
10 depressive symptoms and a high self-rated quality of life at baseline (Table 1). At 36-month follow-
11 up, their depressive symptoms and self-rated quality of life had changed minimally from baseline
12 (Table 2 and 3).
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17 DISCUSSION

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19 This study did not find any long-term effect of an intensive psychosocial intervention
20 (DAISY intervention) on patients and caregivers beyond the effect of structured follow-up support.
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23 To our knowledge, this study is the largest randomised controlled trial of early
24 psychosocial intervention for patients with mild Alzheimer' disease and their caregivers to date,
25 with a long follow-up of three years. It is a study of solid methodology, strictly adhering to
26 CONSORT recommendations. A-priori sample size calculation was done. The measures for
27 primary and secondary outcomes are reliable scales, which are commonly used in routine clinical
28 practice and in intervention studies across cultures.^{26,27} Proper randomisation, allocation
29 concealment, rater-blinded evaluation of outcomes, and adjustment for multiple testing were
30 rigorously carried out to reduce biases that could lead to type I errors.¹¹ The multicomponent semi-
31 tailored intervention programme was intensive in both content and duration, targeted multiple
32 needs, tended to the individual needs, and simultaneously involved caregivers and patients; thus
33 having the characteristics that defined successful intervention programs documented in the
34 literature.^{2,5,7} Since ours was one of the first studies to examine the effect of support and counselling
35 programmes in patients with very mild dementia, no previous consensus exists concerning gold
36 standards for assessing efficacy. Therefore, multiple primary and secondary outcomes were
37 exploratively chosen based on the specific aims of the DAISY intervention and on the outcomes
38 from similar intervention studies for patients with more advanced dementia.¹ Consequently, to
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8 avoid finding spurious effects, a significance level was set at $P = 0.0005$, which was subsequently
9 criticized for being too conservative.¹² All patients in this study had primary caregivers who were
10 very involved in caregiving, a situation that cannot be generalised to all patients with dementia in
11 Denmark.
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15 Although not statistically significant for this adjusted P value, DAISY intervention
16 did produce small positive effects trends on reducing depressive symptoms (~~Cornell depression~~
17 ~~score, $P = 0.0103$~~) and maintaining quality of life for the patients (~~proxy-rated QoL-AD, $P = 0.0013$~~)
18 at 12-month follow-up.¹¹ The effect size of DAISY intervention regarding Cornell depression score
19 was -1.58 (-2.79 to -0.37, $P = 0.0103$) and regarding proxy-rated QoL-AD was 2.14 (0.83 to 3.45; P
20 = 0.0013). The disease-specific QoL-AD is probably more sensitive to measure the effect of
21 psychological interventions than general EQ-VAS.²⁷ At 36-month follow-up, these positive trends
22 effects were no longer present. (~~Cornell depression score, $P = 0.93$; proxy-rated QoL-AD, $P =$~~
23 ~~0.82).~~ Between 12- and 36-month follow-up, there was significant decline in patients' cognition,
24 quality of life, and ADL. During this time period, there was no continuing intervention or support.
25 Initially, the study was intended to end at 12-month follow-up. However, we received additional
26 funding to carry out follow-up at 36 months. The timing and duration of DAISY intervention could
27 have missed a period of significant decline when intervention could have been more beneficial.
28 Possibly, the positive trends observed at the 12-month follow-up could have been maintained or
29 enhanced had the intervention continued an additional two years. Evidence from the very limited
30 literature seems to support the hypothesis that the positive effects of psychosocial interventions
31 could be lost without continuous reinforcement. There are few randomised controlled trials
32 assessing the efficacy of psychosocial intervention that specifically targets community-dwelling
33 patients with dementia.^{6,10} Most trials had short follow-up period, usually three to six months. One
34 trial showed that a three-month programme of intensive physical exercise for the patients combined
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8 with teaching caregivers strategies to manage patients' behavioural problems improved the patients'
9 physical functioning and depressive symptoms.²⁸ At 24-month follow-up, the improvement in
10 physical functioning was still significant, but the improvement of depressive symptoms was no
11 longer present.²⁸ In contrast, another trial with eight-year follow-up reported delayed nursing home
12 placement for patients by providing a multicomponent interventions for the caregivers and patients;
13 the ten-day intervention program was followed by continuous support over the telephone weekly for
14 the first year and yearly thereafter for the next seven years.²⁹

21 In our study, there are some possible explanations for the non-significant positive
22 effects found at 12-month concerning patients' depressive symptoms and quality of life and the
23 disappearance of these effects at 36-month follow-up. First, it could be a floor effect. Our patients
24 had minimal depressive symptoms and relatively high scores of QoL-AD at baseline. A randomised
25 controlled trial using support group intervention for community-dwelling patients with mild
26 Alzheimer's disease and their caregivers showed that patients who experienced improvement in
27 their depressive symptoms had significantly more depressive symptoms at baseline and higher level
28 of distress.³⁰ Second, there was no need assessment at baseline. Probably, participants with more
29 symptoms and at greater need should have received the full intensive intervention programme and
30 regular support follow-up was sufficient for those who had minimal symptoms and needs at
31 baseline. Third, the control group also received some intervention that is much better than the usual
32 practice in Denmark.³¹ They had regular follow-ups when they could speak about emerging
33 psychosocial and health problems, receive information about available resources, and get referred to
34 relevant health professionals if needed. It is noteworthy that despite the marked decline in patients'
35 global cognitive function, quality of life, and ADL between 12- and 36-month follow-ups,
36 participants in both group had minimal changes in mean Cornell Depression Scale scores compared
37 to baseline. This could be an indication that the regular follow-ups offered in this study were

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8 sufficient enough to produce a long-term effect in preventing the conversion into clinical depression
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10 for the patients. Fourth, as mentioned above, the intervention should probably continue
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12 longitudinally following the clinical progression in these patients to show long-term positive
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14 effects. The study did not find any long-term effect on DAISY intervention on the caregiver
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16 outcomes. Previous studies have shown positive responses to interventions from caregivers with
17
18 high levels of depression and anxiety at baseline.¹⁰ For this mostly asymptomatic group of
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20 caregivers in our study, perhaps follow-up at regular intervals provided enough information and
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22 support to prevent the emergence of depressive symptoms and maintain good life quality.

23
24 It is not known why patients in the intervention group had higher mortality than
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26 those in the control group. This increased mortality was unlikely to be caused by the intervention, as
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28 the nature of the intervention program did not subject the patients to any health risk. Using the data
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30 from Statistics Denmark (www.dst.dk), the incidence of death for the age-matched general
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32 population over the same time period was found to be similar to that of the DAISY intervention
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34 group. The control group however had lower incidence of death compared to the general
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36 population. At baseline, the quality of life of the patients in the intervention group was rated as
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38 poorer than that of the control group, both by the patients themselves and by their caregivers (Table
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40 1). Although not statistically significant, there were small socioeconomic and clinical differences
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42 that were in favour of the control group could be responsible for the higher mortality rate in the
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44 intervention groups. More patients in the intervention group lived alone (4% difference), rented
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46 their house (7% difference), had more co-morbidities (4.4% difference), and were diagnosed with
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48 mixed AD and vascular dementia (4.2% difference, Table 1). Whether these differences could
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50 contribute to the higher mortality in the intervention group is uncertain. It is known that older
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52 people living alone have higher mortality than those living with others.³² Currently, there is
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8 insufficient evidence in the literature concerning the effect of psychosocial intervention on patient
9 mortality, as studies looking at this effect are scarce.^{5,33}

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11 The same patient characteristics in the DAISY intervention group stated above could
12 also explain the lack of effect concerning nursing home placement.³⁴ Additionally, continuous
13 intervention and follow-up between 12 and 36 months could have been needed to produce a positive
14 long-term effect on nursing home placement. Randomised controlled trials that reported positive
15 long-term effect of psychosocial intervention on patients' nursing home placement provided
16 continuous support and counselling over the phone for eight-nine years.^{29,35} In contrast, intervention
17 lasting two years but without continuous follow-up and support showed no long-term effect on
18 nursing home placement.³³

19
20 Although this study found no long-term effect of DAISY intervention, a qualitative
21 study linked to this randomised controlled trial showed ~~that promising indications that early~~
22 ~~psychosocial intervention for patient with very mild Alzheimer's disease and their caregivers could~~
23 ~~potentially prevent the emergence of depressive symptoms and maintain the quality of life for the~~
24 ~~patients.~~³⁶ ~~This study revealed that both patients and caregivers found the DAISY intervention~~
25 ~~stimulating and rewarding. 80% of patients and 94% of caregivers in the intervention group found~~
26 ~~the intervention overall beneficial.~~ Patients felt that their self-esteem was improved and they could
27 better manage their daily life and social relations. Caregivers felt that they were more confident and
28 competent to cope with the challenges of caring for relatives with AD. After the intervention, both
29 patients and caregivers looked for support groups to join permanently and caregivers sought
30 continuing counseling.³⁶ ~~In contrast to randomised clinical trials about pharmacological~~
31 ~~interventions, we did not carry out the DAISY study to justify the reason for providing psychosocial~~
32 ~~intervention for patients with dementia and their caregivers, whose needs for information,~~
33 ~~counselling, and support cannot be denied. What we can conclude from this study is that since we~~
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8 could not show positive effects in the quantitative analyses, we should not offer psychosocial
9 intervention indiscriminately to all patients with very mild dementia and their caregivers, but we
10 should probably assess their needs and offer intervention only to those who need. Regular follow-up
11 is therefore important to identify the arising needs that require intervention. Probably, The lessons
12 learned from this study is that the ~~type~~ content, dose and intensity, and duration of early intervention
13 ~~should~~ be more tailored to match the needs of patients and their caregivers at baseline to
14 maximize benefit, economize resources, and avoid unnecessary intervention burden. Need
15 assessment is of primary importance. The intervention program should perhaps be designed so that
16 patients and caregivers with greater needs at baseline receive more intensive interventions that cater
17 to their specific needs, those with lesser needs receive a basic intervention program of lower
18 intensity, and those with minimal or no needs receive no intervention at all. Regular follow-up
19 assessment is necessary to identify emerging needs. To obtain long-term effect, early intervention
20 should probably have a longitudinal and fluid course that follows the disease progression, being
21 continuously modified according to the needs that arise. These are the questions to be answered in
22 future studies.

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Figure 1: Trial flow for Danish Alzheimer Intervention Study (DAISY)

¹ Patients and caregivers. ² Full compliance is defined as participation from both the caregiver and the patient in at least 3 courses and 3 counselling sessions each. ³ In the analysis accounting for drop outs, information from all participating dyads were incorporated.

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Table 1: Baseline characteristics of patients with Alzheimer's disease and their caregivers who participated in the Danish Alzheimer Intervention Study (DAISY). Values are numbers (percentages) of participants unless stated otherwise

Patients' characteristics	Intervention (n=163)	Control (n=167)
Sex		
Male	76 (46.6)	75 (44.9)
Female	87 (53.4)	92 (55.1)
Mean (SD) age (years)	76.5 (7.7)	75.9 (6.6)
Household status		
Living alone	54 (33.1)	48 (28.7)
Living with others	109 (66.9)	119 (71.3)
Home		
Rented	66 (40.5)	56 (33.5)
Owned	97 (59.5)	111 (66.5)
Education		
None	60 (36.8)	57 (34.1)
< 3 years	39 (23.9)	49 (29.3)
≥ 3 years	64 (39.3)	61 (36.5)
Charlson comorbidity index		
No comorbidity	64 (39.3)	73 (43.7)
One comorbidity	75 (46.0)	65 (38.9)
≥ 2 comorbidities	24 (14.7)	29 (17.4)
Diagnosis		
Pure Alzheimer's disease	112 (68.7)	127 (76.1)
Mixed Alzheimer's disease and vascular dementia	44 (27.0)	38 (22.8)
Lewy body dementia	7 (4.3)	2 (1.2)
Caregiver' characteristics		
Sex		
Male	54 (33.1)	56 (33.5)
Female	109 (66.9)	111 (66.5)
Mean (SD) age (years)	65.5 (12.7)	66.5 (12.7)
Relation		
Spouse	104 (63.8)	111 (66.5)
Child or child in law	45(27.6)	41(24.5)
Other	14 (8.6)	15 (9.0)
Living with patient		
Yes	101/162 (62.4)	112/166 (67.5)
No	61/162 (37.6)	54/166 (32.5)
Home		
Rent	45 (27.6)	45 (26.9)
Own	118 (72.4)	122 (73.1)
Education		

None	41 (25.2)	37/166 (22.3)
< 3 years	46 (28.2)	63/166 (37.9)
≥ 3 years	76 (46.6)	66 /166 (39.8)
Outcome measures at baseline		
Primary patient outcomes		
Mean (SD) MMSE	24.0 (2.5)	24.1 (2.7)
Mean (SD) Cornell Depression Scale	5.2 (4.8)	4.4 (4.0)
Mean (SD) proxy-rated EQ-VAS	62.1 (18.4) (n=162)	64.7 (20.4)
Primary caregiver outcome		
Mean (SD) EQ-VAS	79.3 (16.3) (n=162)	81.4 (16.3)
Mean (SD) GDS	4.74 (5.2) (n=162)	4.71 (5.0)
Secondary patient outcome		
Mean (SD) QoL-AD (proxy-rated)	33.0 (6.1)	34.7 (6.6)
Mean (SD) NPI-Q	3.9 (3.6)	3.9 (3.7)
Mean (SD) ADSC-ADL	61.2 (11.4)	61.8 (11.4)

MMSE: Mini Mental State Examination. EQ-VAS: European Quality of Life Visual Analogue Scale. GDS: Geriatric Depression Scale. QoL-AD: Quality of Life Scale for Alzheimer's Disease. NPI-Q: Neuropsychiatric Inventory Questionnaire. ADSC-ADL: Alzheimer's Disease Cooperative Study Activities of Daily Living Scale.

Table 2: Outcome measures of DAISY psychosocial interventions based on completed response at 36-month follow-up. Values are means (SD) unless stated otherwise.

	Observed scores		Changes from baseline	
	Intervention	Control	Intervention	Control
Primary patient outcomes				
MMSE	17.8 (6.7) (n=84)	17.9 (7.1) (n=94)	-6.21 (6.17) (n=84)	-6.35 (6.26) (n=94)
Cornell Depression Scale	5.57 (4.78) (n=93)	5.17 (4.19) (n=101)	1.29 (4.94) (n=93)	0.74 (4.45) (n=101)
Proxy-rated EQ-VAS	50.7 (20.3) (n=95)	52.3 (21.0) (n=102)	-12.88 (20.3) (n=95)	-12.46 (19.0) (n=102)
Primary caregiver outcomes				
EQ-VAS	79.4 (16.1) (n=94)	79.0 (18.0) (n=103)	-0.79 (16.5) (n=94)	-1.49 (16.5) (n=103)
GDS	5.26 (5.43) (n=94)	4.51 (5.26) (n=103)	0.81 (4.83) (n=94)	0.14 (4.52) (n=103)
Secondary patient outcomes				
QoL-AD (proxy-rated)	30.5 (5.1) (n=96)	32.1 (6.2) (n=103)	-2.89 (4.89) (n=96)	-2.84 (-2.00) (n=103)
NPI-Q	5.21 (4.43) (n=96)	5.05 (4.80) (n=104)	1.57 (4.43) (n=96)	1.20 (4.68) (n=104)
ADSC-ADL	35.3 (19.4) (n=96)	41.3 (20.8) (n=104)	-26.7 (16.6) (n=96)	-22.3 (19.6) (n=104)

MMSE: Mini Mental State Examination. EQ-VAS: European Quality of Life Visual Analogue Scale. GDS: Geriatric Depression Scale. QoL-AD: Quality of Life Scale for Alzheimer's Disease. NPI-Q: Neuropsychiatric Inventory Questionnaire. ADSC-ADL: Alzheimer's Disease Cooperative Study Activities of Daily Living Scale.

Table 3: Outcomes of DAISY psychosocial interventions based on inverse probability weighting of respondents with non-missing data at 36-month follow up (intention to treat analyses adjusted for attrition). Values are means* (95% CI) unless stated otherwise.

	Estimated endpoint scores			Mean change from baseline		
	Intervention	Control	P value of t test	Intervention	Control	P value of t test
Primary patient outcomes:						
MMSE	18.0 (16.5 to 19.6)	18.1 (16.4 to 19.8)	0.96	-6.57 (-7.89 to -5.25)	-6.56 (-7.98 to -5.14)	0.99
Cornell Depression Scale	4.89 (3.75 to 6.03)	4.20 (3.10 to 5.31)	0.32	0.59 (-0.49 to 1.66)	0.64 (-0.21 to 1.49)	0.93
Proxy-rated EQ-VAS	55.9 (51.0 to 60.8)	60.1 (54.6 to 65.6)	0.20	-12.44 (-16.64 to -8.24)	-10.77 (-15.19 to -6.35)	0.59
Primary caregiver outcome						
EQ-VAS	80.3 (76.2 to 84.3)	79.5 (74.5 to 84.6)	0.78	0.14 (-3.18 to 3.47)	-2.71 (-6.66 to 1.23)	0.28
GDS	5.83 (4.27 to 7.38)	4.98 (3.43 to 6.53)	0.29	0.47 (-0.58 to 1.52)	-0.33 (-1.39 to 0.72)	0.29
Secondary patient outcome						
QoL-AD (proxy-rated)	31.0 (29.3 to 32.6)	32.8 (31.2 to 35.3)	0.03	-2.83 (-3.85 to -1.80)	-2.64 (-3.82 to -1.46)	0.82
NPI-Q	4.90 (3.85 to 5.96)	4.73 (3.53 to 5.93)	0.79	1.48 (0.55 to 2.40)	1.30 (0.37 to 2.23)	0.80
ADSC-ADL	34.1 (29.1 to 39.2)	39.9 (35.1 to 44.7)	0.05	-26.9 (-30.8 to -22.9)	-21.7 (-25.6 to -17.7)	0.07

MMSE: Mini Mental State Examination. EQ-VAS: European Quality of Life Visual Analogue Scale. GDS: Geriatric Depression Scale. QoL-AD: Quality of Life Scale for Alzheimer's Disease. NPI-Q: Neuropsychiatric Inventory Questionnaire. ADSC-ADL: Alzheimer's Disease Cooperative Study Activities of Daily Living Scale.

*Means are estimated from a longitudinal model where selective dropout is accounted for by inverse probability weighting; the inclusion of a categorical indicator variable for treating centre accounts for possible clustering within centre; confidence intervals and P values are calculated with generalised estimating equations.

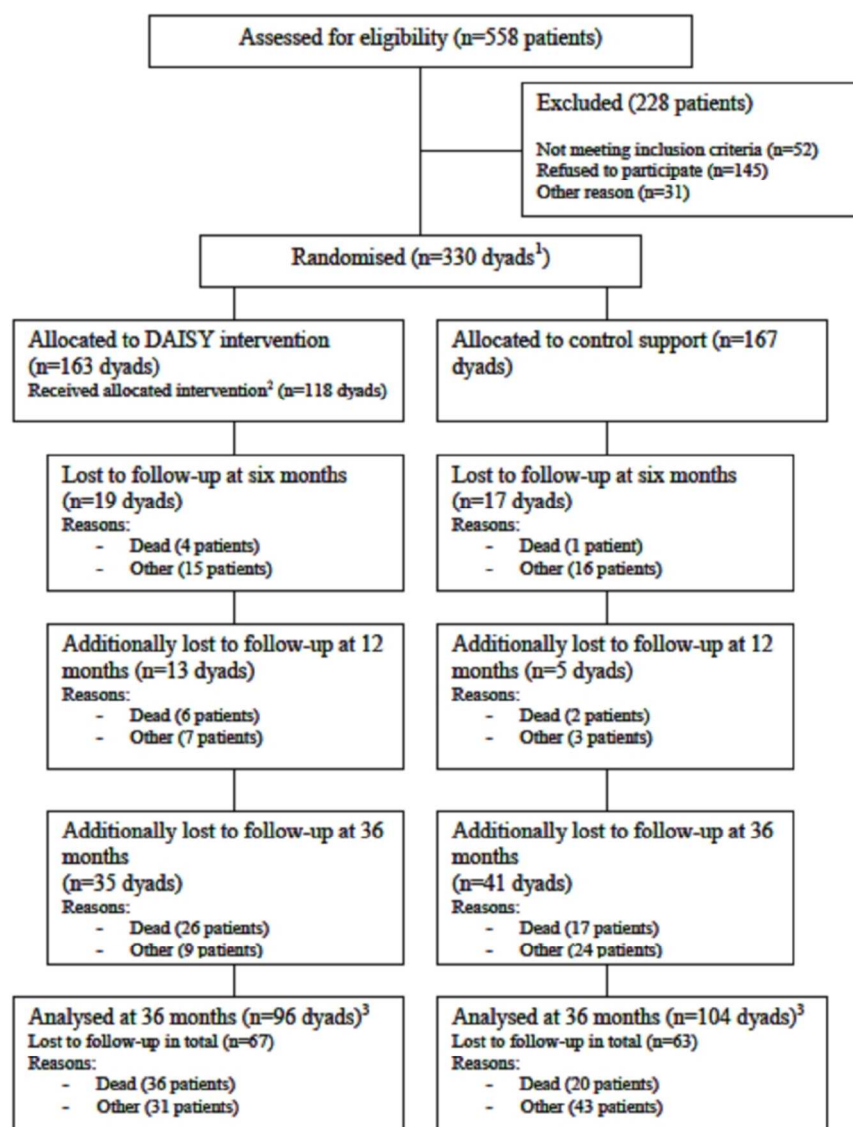


Figure 1: Trial flow for Danish Alzheimer Intervention Study (DAISY)
90x110mm (300 x 300 DPI)

Table 2 (alternative): Outcome of DAISY psychosocial interventions based on completed response at 36-month follow-up. All analyses were intention-to-treat.

	Observed scores		Change from baseline		Differences in scores, intervention versus control*	
	Intervention	Control	Intervention	Control	Mean (95%CI)	P-value
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)		
Primary patient outcomes						
MMSE	17.8 (6.7) (n=84)	17.9 (7.1) (n=94)	-6.21 (6.17) (n=84)	-6.35 (6.26) (n=94)	0.19 (-2.30 to 2.71)	0.89
Cornell Depression Scale	5.57 (4.78) (n=93)	5.17 (4.19) (n=101)	1.29 (4.94) (n=93)	0.74 (4.45) (n=101)	0.47 (-0.68 to 1.61)	0.42
EQ-VAS (proxy-rated)	50.7 (20.3) (n=95)	52.3 (21.0) (n=102)	-12.88 (20.3) (n=95)	-12.46 (19.0) (n=102)	-0.95 (-3.97 to 2.07)	0.54
Primary caregiver outcome						
EQ-VAS	79.4 (16.1) (n=94)	79.0 (18.0) (n=103)	-0.79 (16.5) (n=94)	-1.49 (16.5) (n=103)	0.53 (-2.08 to 3.15)	0.69
GDS	5.26 (5.43) (n=94)	4.51 (5.26) (n=103)	0.81 (4.83) (n=94)	0.14 (4.52) (n=103)	0.70 (-0.31 to 1.70)	0.17
Secondary patient outcome						
QoL-AD (proxy-rated)	30.5 (5.1) (n=96)	32.1 (6.2) (n=103)	-2.89 (4.89) (n=96)	-2.84 (-2.00) (n=103)	-0.70 (-1.57 to 0.16)	0.11
NPI-Q	5.21 (4.43) (n=96)	5.05 (4.80) (n=104)	1.57 (4.43) (n=96)	1.20 (4.68) (n=104)	0.27 (-0.59 to 1.13)	0.54
ADSC-ADL	35.3 (19.4) (n=96)	41.3 (20.8) (n=104)	-26.7 (16.6) (n=96)	-22.3 (19.6) (n=104)	-4.74 (-8.12 to -1.35)	0.01

MMSE: Mini Mental State Examination. EQ-VAS: European Quality of Life Visual Analogue Scale. GDS: Geriatric Depression Scale. QoL-AD: Quality of Life Scale for Alzheimer's Disease. NPI-Q: Neuropsychiatric Inventory Questionnaire. ADSC-ADL: Alzheimer's Disease Cooperative Study Activities of Daily Living Scale.

*The mean difference in outcome attributable to the randomisation is assessed in an analysis of covariance where the primary comparison between randomisation groups is adjusted for the baseline value of the corresponding outcome in a multivariable linear regression model; the confidence intervals (95% CI) and P-values corresponding to these differences are calculated using generalised estimating equations to account for correlation within treating centre.



CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	5
	2b	Specific objectives or hypotheses	6
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	6
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	NA
Participants	4a	Eligibility criteria for participants	7
	4b	Settings and locations where the data were collected	7
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	7
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	8,9,10
	6b	Any changes to trial outcomes after the trial commenced, with reasons	NA
Sample size	7a	How sample size was determined	6
	7b	When applicable, explanation of any interim analyses and stopping guidelines	NA
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	6
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	6
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	6,11
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	6,7
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	6,10,11

1			
2		assessing outcomes) and how	
3			
4		11b If relevant, description of the similarity of interventions	
5	Statistical methods	12a Statistical methods used to compare groups for primary and secondary outcomes	11
6		12b Methods for additional analyses, such as subgroup analyses and adjusted analyses	11
7			
8	Results		
9	Participant flow (a	13a For each group, the numbers of participants who were randomly assigned, received intended treatment, and	Figure 1
10	diagram is strongly	were analysed for the primary outcome	
11	recommended)	13b For each group, losses and exclusions after randomisation, together with reasons	Figure 1,
12	Recruitment	14a Dates defining the periods of recruitment and follow-up	
13		14b Why the trial ended or was stopped	7
14			
15	Baseline data	15 A table showing baseline demographic and clinical characteristics for each group	Table 1
16	Numbers analysed	16 For each group, number of participants (denominator) included in each analysis and whether the analysis was	
17		by original assigned groups	Table 2
18			
19	Outcomes and	17a For each primary and secondary outcome, results for each group, and the estimated effect size and its	
20	estimation	precision (such as 95% confidence interval)	Table 3,
21			pages 11-13
22		17b For binary outcomes, presentation of both absolute and relative effect sizes is recommended	NA
23	Ancillary analyses	18 Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing	Table 2 and 3
24		pre-specified from exploratory	
25			
26	Harms	19 All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	12,16
27			
28	Discussion		
29	Limitations	20 Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	13,14
30	Generalisability	21 Generalisability (external validity, applicability) of the trial findings	14
31	Interpretation	22 Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	14,15,16,17
32			
33	Other information		
34	Registration	23 Registration number and name of trial registry	1
35	Protocol	24 Where the full trial protocol can be accessed, if available	6
36	Funding	25 Sources of funding and other support (such as supply of drugs), role of funders	19
37			

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.