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

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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.

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

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 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

- 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 responsibly 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

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

Intervention

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

The patients in the intervention and the control groups were followed up at 3, 6, 12, and 36 months, when they were inquired about their symptoms and daily activities and informed

about available support programmes in their local communities, which they could freely take part in. Furthermore, health care needs were identified and participants were referred to local health professionals if necessary.

Outcomes

Primary outcomes for the patients:

1. Global cognitive function: The patient's global cognitive function was assessed using Mini Mental State Examination (MMSE).[13] The sum of scores ranges from 0 to 30. Higher scores indicate better cognitive function.
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 System[24] 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 $\chi 2$ tests for categorical variables. With linear models on the full data of up to four observations per dyad, we compared the difference in development of the primary and secondary outcomes between randomisation groups during the follow-up period, using generalised estimating equations to account for repeated measurements; the inclusion of a categorical centre indicator variable account for possible clustering by treating centre. To adjust for possible bias because of differential death and dropout from the study between the intervention and control groups, the assessments at the various follow-up times were weighted by the inverse of an estimate of the probability of staying in the study.[25] These probabilities were estimated from the data in logistic regression models for death and dropout with the dyads' characteristics and the observed primary outcomes from previous visits as covariates. Only the expected scores and inferences for the 36-month follow-up were reported. Differences in mortality and nursing home placement rates between the two groups were evaluated by a hazard ratio (HR) from a Cox regression model. All analyses were done using the intention-to-treat principle.

RESULTS

558 patients were screened for eligibility and 330 patient-caregiver dyads were included: 163 were randomized to DAISY intervention group and 167 to control group (Figure 1). Their demographics, clinical characteristics, and outcome measures at baseline are provided in

Table 1. Most patients received cognition enhancing medications (93.3 % cholinesterase inhibitor and 1% NMDA receptor antagonist).[1] Overall, the participation rate in the DAISY intervention group was high.[11]

At 36 months, a total of 130 patients (67 in the intervention group and 63 in the control group) were lost to follow up (Figure 1). In all, 56 patients had deceased, 36 from the DAISY intervention group and 20 from the control group (Figure 1). Patients in the DAISY intervention had a higher mortality rate (HR 1.99; 95% CI: 1.15 to 3.43; P = 0.01). Regarding nursing home placement, 43 patients from DAISY intervention group and 48 from the control group were placed in nursing homes at 36-month follow-up. Data on nursing home placement was missing for five participants in the intervention group. There was no difference between the rates of nursing home placement for the intervention and control groups (HR 0.97; 95% CI: 0.64 to 1.47; P = 0.89).

As reported previously, the 12-month follow-up study observed positive trends concerning the effect of DAISY intervention on preventing the emergence of depressive symptoms (Cornell depression scale, primary patient outcome) and maintaining quality of life (proxy-rated QoL-AD, secondary patient outcome).[11] In this 36-month follow-up study, which took place after the DAISY interventions had stopped for two years, there was no significant difference in 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). 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.

To our knowledge, this study 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. A-priori sample size calculation was done. The measures for primary and secondary outcomes are reliable scales, which are commonly used in routine clinical practice and in intervention studies across cultures.[26,27] Proper randomisation, allocation concealment, rater-blinded evaluation of outcomes, and adjustment for multiple testing were rigorously carried out to reduce biases that could lead to type I errors.[11] 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.[2,5,7] Since ours was one of the first studies to examine the effect of support and counselling

programmes in patients with very mild dementia, no previous consensus exists concerning gold standards for assessing efficacy. Therefore, multiple primary and secondary outcomes were exploratively chosen based on the specific aims of the DAISY intervention and on the outcomes from similar intervention studies for patients with more advanced dementia.[1] Consequently, to avoid finding spurious effects, a significance level was set at P = 0.0005, which was subsequently criticized for being too conservative.[12] All patients in this study had primary caregivers who were very involved in caregiving, a situation that cannot be generalised to all patients with dementia in Denmark.

Although not statistically significant for this P value, DAISY intervention did produce small positive trends on reducing depressive symptoms (Cornell depression score, P=0.0103) and maintaining quality of life for the patients (proxy rated QoL-AD, P=0.0013) at 12-month follow-up.[11] The disease-specific QoL-AD is probably more sensitive to measure the effect of psychological interventions than general EQ-VAS.[27] At 36-month follow-up, these positive trends were no longer present (Cornell depression score, P = 0.93; proxy-rated QoL-AD, P = 0.82). 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

dementia.[6,10] Most trials had short follow-up period, usually three to six months. One trial showed that a three-month programme of intensive physical exercise for the patients combined with teaching caregivers strategies to manage patients' behavioural problems improved the patients' physical functioning and depressive symptoms.[28] At 24-month follow-up, the improvement in physical functioning was still significant, but the improvement of depressive symptoms was no longer present.[28] In contrast, another trial with eight-year follow-up reported delayed nursing home placement for patients by providing a multicomponent interventions for the caregivers and patients; the ten-day intervention program was followed by continuous support over the telephone weekly for the first year and yearly thereafter for the next seven years.[29]

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

participants in both group had minimal changes in mean Cornell Depression Scale scores compared to baseline. This could be an indication that the regular follow-ups offered in this study were sufficient enough to produce a long-term effect in preventing the conversion into clinical depression for the patients. Fourth, as mentioned above, the intervention should probably continue longitudinally following the clinical progression in these patients to show long-term positive effects. The study did not find any long-term effect on DAISY intervention on the caregiver outcomes. Previous studies have shown positive responses to interventions from caregivers with high levels of depression and anxiety at baseline.[10] For this mostly asymptomatic group of caregivers in our study, perhaps follow-up at regular intervals provided enough information and support to prevent the emergence of depressive symptoms and maintain good life quality.

Patients in the intervention group had higher mortality than those in the control group. This increased mortality was unlikely to be caused by the intervention, as the nature of the intervention program did not subject the patients to any health risk. Using the data from Statistics Denmark (www.dst.dk), the incidence of death for the age-matched general population over the same time period was found to be similar to that of the DAISY intervention group. The control group however had lower incidence of death compared to the general population. At baseline, the quality of life of the patients in the intervention group was rated as poorer than that of the control group, both by the patients themselves and by their caregivers (Table 1). Although not statistically significant, there were socioeconomic and clinical differences that were in favour of the control group. More patients in the intervention group lived alone (4% difference), rented their house (7% difference), had more co-morbidities (4.4% difference), and were diagnosed with mixed AD and vascular dementia (4.2% difference, Table 1). Whether these differences could contribute to the higher mortality in the intervention group is uncertain. It is known that older people living alone have higher mortality than those living with others.[32] Currently, there is insufficient evidence in the

literature concerning the effect of psychosocial intervention on patient mortality, as studies looking at this effect are scarce.[5,33] The same patient characteristics in the DAISY intervention group stated above could also explain the lack of effect concerning nursing home placement.[34] Additionally, continuous intervention and follow-up between 12 and 36 months could have been needed to produce a positive long-term effect on nursing home placement. Randomised controlled trials that reported positive long-term effect of psychosocial intervention on patients' nursing home placement provided continuous support and counselling over the phone for eight-nine years.[29,35] In contrast, intervention lasting two years but without continuous follow-up and support showed no long-term effect on nursing home placement.[33]

Although this study found no long-term effect of DAISY intervention, a qualitative study linked to this randomised controlled trial showed promising indications that early psychosocial intervention for patient with very mild Alzheimer's disease and their caregivers could potentially prevent the emergence of depressive symptoms and maintain the quality of life for the patients.[36] This study revealed that both patients and caregivers found the DAISY intervention stimulating and rewarding. Patients felt that their self-esteem was improved and they could better manage their daily life and social relations. Caregivers felt that they were more confident and competent to cope with the challenges of caring for relatives with AD. After the intervention, both patients and caregivers looked for support groups to join permanently and caregivers sought continuing counseling.[36] The lessons learned from this study is that the content, dose and intensity, and duration of early intervention can be more tailored to match the needs of patients and their caregivers at baseline to maximize benefit, economize resources, and avoid unnecessary intervention burden. Need assessment is of primary importance. The intervention program should perhaps be designed so that patients and caregivers with greater needs at baseline receive more intensive interventions that cater to their specific needs, those with lesser needs receive a basic

intervention program of lower intensity, and those with minimal or no needs receive no intervention at all. Regular follow-up assessment is necessary to identify emerging needs. To obtain long-term effect, early intervention should probably have a longitudinal and fluid course that follows the disease progression, being continuously modified according to the needs that arise. These are the questions to be answered in future studies.

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Contributorship: KP drafted the manuscript. FBW, VS, NK, MLHR, and GW outlined the statistical analysis. VS conducted the statistical analysis in consultation with NK. FBW, AE, DVB, AV and GW designed and conducted the DAISY study. KP, FBW, and GW worked with interpretation of data analysis. All authors assisted in editing this manuscript. All authors read and approved the final manuscript. All authors are guarantors for the scientific integrity of the articles.

References

1. Waldemar G, Waldorff FB, Buss DV, et al. The Danish Alzheimer intervention study: rationale, study design and baseline characteristics of the cohort. Neuroepidemiology. 2011;**36**:52-61.

2. Schulz R, Martire LM. Family caregiving of persons with dementia: prevalence, health effects, and support strategies. Am J Geriatr Psychiatry. 2004;**12**:240-9. Review.

3. van der Roest HG, Meiland FJ, Maroccini R, et al. Subjective needs of people with dementia: a review of the literature. Int Psychogeriatr. 2007;**19**:559-92.

4. Gaugler JE, Kane RL, Kane RA, et al. Unmet care needs and key outcomes in dementia J Am Geriatr Soc. 2005;**53**:2098-105.

5. Brodaty H, Green A, Koschera A. Meta-analysis of psychosocial interventions for caregivers of people with dementia. J Am Geriatr Soc 2003;**51**:657-64.

6. Brodaty H, Arasaratnam C. Meta-analysis of nonpharmacological interventions for neuropsychiatric symptoms of dementia. Am J Psychiatry. 2012;**169**:946-53.

7. Pinquart M, Sorensen S. Helping caregivers of persons with dementia: which interventions work and how large are their effects? Int Psychogeriatr 2006;**18**:577-95.

8. Thompson CA, Spilsbury K, Hall J, et al. Systematic review of information and support interventions for caregivers of people with dementia. BMC Geriatr 2007;7:18.

9. Schoenmakers B, Buntinx F, DeLepeleire J. Supporting the dementia family caregiver: the effect of home care intervention on general well-being. Aging Ment Health. 2010;**14**:44-56. Review.

10. Olazarán J, Reisberg B, Clare L, et al. Nonpharmacological therapies in Alzheimer's disease: a systematic review of efficacy. Dement Geriatr Cogn Disord. 2010;**30**:161-78.

11. Waldorf FB, Buss DV, Eckermann A, et al. Efficacy of psychosocial intervention in patients with mild Alzheimer's disease: the multicentre, rater blinded, randomised Danish Alzheimer Intervention Study (DAISY). BMJ Published Online First: 17 July 2012. doi: 10.1136/bmj.e4693.

12. Mittelman MS. The DAISY psychosocial intervention does not improve outcomes in patients with mild Alzheimer's disease or their carers. Evid Based Ment Health. 2013 Feb;**16**:15.

13. Folstein MF, Folstein SE, McHugh PR. "Mini-mental State". J Psychiat Res 1975;**12**:189-198.

14. American Psychiatric Association (APA). Diagnostic and Statistical Manual of Mental Disorders. DSM-IV, 4th edition. Washington, D.C., American Psychiatric Association, 1993

15. McKhann G, Drachman D, Folstein M, et al. Clinial diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984;**34:**939-944.

16. McKeith IG, Galasko D, Kosaka K, et al. Consensus guidelines for the clinical and pathological diagnosis of dementia with Lewy bodies (DLB): Report of the consortium on DLB international workshop. Neurology 1996;**47**:1113-1124.

17. Peavey VR. Sociodynamic Counseling: A Constructivist Perspective for the Practice of counselling in the 21st Century. Victoria. Trafford Publishing: 1997.

18. Alexopoulos GS, Abrams RC, Young RC, et al. Cornell scale for depression in dementia. Biol Psychiatry 1988;23:271-84.

19. The EuroQoL Group. EuroQoL-a new facility for the measurement of health-related quality of life. Health Policy 1990;**1**:199-208.

20. Yesavage JA, Brink TL, Rose TL, Lum O, Huang V, Adey M, et al. Development and validation of a geriatric depression screening scale: a preliminary report. J Psychiatr Res 1982;**17**:37-49.

21. Logsdon RG, Gibbons LE, McCurry S, Teri L. Quality of life in Alzheimer's disease: patient and caregiver report (QoL-AD). J Ment Health Aging 1999;**5**:21-32.

22. Kaufer DI, Cummings JL, Ketchel P, et al. Validation of the NPI-Q, a brief clinical form of the neuropsychiatric inventory. J Neuropsychiatry Neurosci 2000;**12**:233-239.

23. Galasko D, Bennett D, Sano M, et al. An inventory to assess activities of daily living for clinical trials in Alzheimer's disease. The Alzheimer's Disease Cooperative Study. Alzheimer Dis Ass Dis 1997;**11(Suppl.2)**:S33-S39.

24. Pedersen CB, Gøtzsche H, Møller JØ, et al. The Danish Civil Registration System. Dan Med Bull 2006;**53**:441-449.

25. Dufouil C, Brayne C, Clayton D. Analysis of longitudinal studies with death and drop-out: a case study. Statistics in Medicine 2004;**23**:2215-2226.

26. Verhey FR, Houx P, Van Lang N, et al. Cross-national comparison and validation of the Alzheimer's Disease Assessment Scale: results from the European Harmonization Project for Instruments in Dementia (EURO-HARPID). Int J Geriatr Psychiatry. 2004;**19**:41-50.

27. Moniz-Cook E, Vernooij-Dassen M, Woods R, et al; INTERDEM group. A European consensus on outcome measures for psychosocial intervention research in dementia care. Aging Ment Health. 2008;**12**:14-29.

28. Teri, L., Gibbons, L.E., McCurry, et al. Exercise plus behavioral management in patients with Alzheimer disease: a randomized controlled trial. JAMA 2003;**290**:2015–2022.

29. Brodaty, H., Gresham,M., Luscombe, G. The Prince Henry Hospital dementia caregivers' training programme. Int. J. Geriatr. Psychiatry 1997;**12:**183–192.

30. Logsdon RG, Pike KC, McCurry SM, et al. Early-stage memory loss support groups: outcomes from a randomized controlled clinical trial. J Gerontol B Psychol Sci Soc Sci. 2010;**65**:691-7.

31. Phung TK, Andersen BB, Kessing LV, et al. Diagnostic evaluation of dementia in the secondary health care sector. Dement Geriatr Cogn Disord 2009;**27**:534-542.

32. Lund R, Due P, Modvig J, et al. Cohabitation and marital status as predictors of mortality--an eight year follow-up study. Soc Sci Med. 2002;**55**:673-9.

33. Brodaty H, Mittelman M, Gibson L, et al. The effects of counselling spouse caregivers of people with Alzheimer disease taking donepezil and of country of residence on rates of admission to nursing homes and mortality. Am J Geriatr Psychiatry. 2009;**17**:734-43.

34. Wattmo C, Wallin AK, Londos E, et al. Risk factors for nursing home placement in Alzheimer's disease: a longitudinal study of cognition, ADL, service utilization, and cholinesterase inhibitor treatment. Gerontologist. 2011;**51:**17-27.

35. Mittelman MS, Haley WE, Clay OJ, et al. Improving caregiver well-being delays nursing home placement of patients with Alzheimer disease. Neurology. 2006;**67**:1592-9.

36. Sørensen LV, Waldorff FB, Waldemar G. Early counselling and support for patient with mild Alzheimer's disease and their caregivers. A qualitative study on outcome. Aging Ment Health 2008;**12**:444-450.

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.

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.

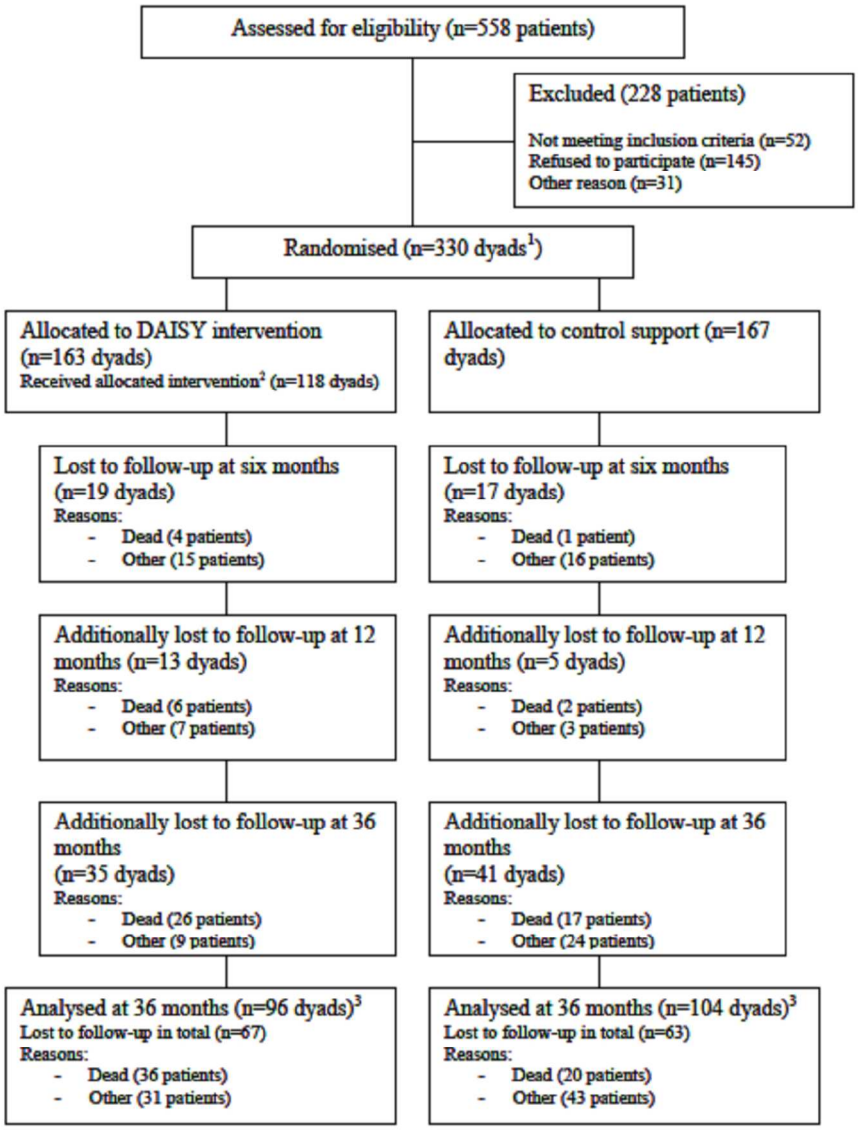

Figure 1: Trial flow for Danish Alzheimer Intervention Study (DAISY)
396x486mm (96 x 96 DPI)

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 (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (95%CI)	P-value
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

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

*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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Primary Subject Heading:	Neurology
Secondary Subject Heading:	Evidence based practice
Keywords:	Dementia < NEUROLOGY, Depression & mood disorders < PSYCHIATRY, Clinical trials < THERAPEUTICS

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

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

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Keywords : Randomised controlled trial, psychosocial, intervention study, dementia, caregivers

Word count: Abstract 296, manuscript 4206

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 responsibly 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] Before adjustment for multiple testing was carried out, the data analysis of the results at 12-month follow-uphad shown statistical significance 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 outcomes. 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

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

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

Intervention

A multifaceted and semi-tailored psychosocial intervention programme, described in details in our previous resports,[1,11] was designed to provide counselling, information, and support to patients with mild dementia and their caregivers in the intervention group. The study coordinator in each centre, an experienced nurse specialising in caring for patients with dementia and having received special training in counselling for the study (constructivist approach),[17] implemented the intervention within the first month after inclusion in the trial. Consisting of five key components, the intervention focused on positive resources, intact function, retained skills, and feasible activities for the patients: 1) The study coordinator provided seven individual counselling sessions tailored to the needs of the patients and their caregivers: two for the patient alone, two for the caregiver alone, two for the patient-caregiver dyad, and one with the dyad together with their family network (optional); 2) The study coordinator provided outreach telephone counselling 5-8 times with 3-4 week intervals to maintain regular contact and follow up on the individual counselling sessions; 3) Using log books, the patients and their caregivers independently kept track of the thoughts and daily issues that they wanted to discuss at the counselling sessions; 4) Experts in the field of dementia were invited to teach five standard courses as group intervention with separate courses for patients and caregivers to provide general information about dementia and forum for discussion, sharing information, and support; 5) Patients and caregivers were provided with information folders produced especially for the purpose of the study about dementia causes, diagnosis and treatment, legal issues, and resources for social support. The intervention program lasted 8 to 12 months. Full

compliance was defined as adherence with the major components of the intervention program: Patients who participated with their caregivers in at least 3 counselling sessions (not including the optional network session) and in at least 3 teaching course sessions.

The patients in both the intervention and the control groups were followed up at 3, 6, 12, and 36 months. Attempts were made to provide similar treatment for both intervention and control participants in all respects other than the add-on DAISY intervention. At each follow-up visit, participants in both groups were interviewed about their current symptoms and daily life issues, and informed about available support program (if any) in their local communities. Both groups were free to participate in such support programs during the study and participation in these support activities was registered for both groups. Identified special needs led to referral to local care facilities when available and relevant.

Outcomes

Primary outcomes for the patients:

1. Global cognitive function: The patient's global cognitive function was assessed using Mini Mental State Examination (MMSE).[13] The sum of scores ranges from 0 to 30. Higher scores indicate better cognitive function.
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 System[24] 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 $\chi 2$ tests for categorical variables. With linear models on the full data of up to four observations per dyad, we compared the difference in development of the primary and secondary outcomes between randomisation groups during the follow-up period, using generalised estimating equations to account for repeated measurements; the inclusion of a categorical centre indicator variable account for possible clustering by treating centre. To adjust for possible bias because of differential death and dropout from the study between the intervention and control groups, the assessments at the various follow-up times were weighted by the inverse of an estimate of the probability of staying in the study, a method explained in the seminal paper by Dufoil et al.[25] These probabilities were estimated from the data in logistic regression models for death and dropout with the dyads'

characteristics and the observed primary outcomes from previous visits as covariates. Only the expected scores and inferences for the 36-month follow-up were reported. Differences in mortality and nursing home placement rates between the two groups were evaluated by a hazard ratio (HR) from a Cox regression model. All analyses were done using the intention-to-treat principle.

RESULTS

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

At 36 months, a total of 130 patients (67 in the intervention group and 63 in the control group) were lost to follow up (Figure 1). In all, 56 patients had deceased, 36 from the DAISY intervention group and 20 from the control group (Figure 1). Patients in the DAISY intervention had a higher mortality rate (HR 1.99; 95% CI: 1.15 to 3.43; P = 0.01). Regarding nursing home placement, 43 patients from DAISY intervention group and 48 from the control group were placed in nursing homes at 36-month follow-up. Data on nursing home placement was missing for five participants in the intervention group. There was no difference between the rates of nursing home placement for the intervention and control groups (HR 0.97; 95% CI: 0.64 to 1.47; P = 0.89).

As reported previously, the 12-month follow-up study observed positive effects of DAISY intervention on preventing the emergence of depressive symptoms (Cornell depression scale, primary patient outcome) and maintaining quality of life (proxy-rated QoL-AD, secondary patient outcome).[11] The effect size of DAISY intervention regarding Cornell depression score 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 =

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.

To our knowledge, this study 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. A-priori sample size calculation was done. The measures for primary and secondary outcomes are reliable scales, which are commonly used in routine clinical practice and in intervention studies across cultures.[26,27] Proper randomisation, allocation concealment, rater-blinded evaluation of outcomes, and adjustment for multiple testing were rigorously carried out to reduce biases that could lead to type I errors.[11] 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.[2,5,7] Since ours was one of the first studies to examine the effect of support and counselling programmes in patients with very mild dementia, no previous consensus exists concerning gold standards for assessing efficacy. Therefore, multiple primary and secondary outcomes were exploratively chosen based on the specific aims of the DAISY intervention and on the outcomes from similar intervention studies for patients with more advanced dementia.[1] Consequently, to avoid finding spurious effects, a significance level was set at P = 0.0005, which was subsequently criticized for being too conservative.[12] All patients in this study had primary caregivers who were very involved in caregiving, a situation that cannot be generalised to all patients with dementia in Denmark.

Although not statistically significant for this adjusted P value, DAISY intervention did produce small positive effects on reducing depressive symptoms and maintaining quality of life for the patients at 12-month follow-up.[11] The effect size of DAISY intervention regarding Cornell depression score 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 = 0.0013). The disease-specific QoL-AD is probably more sensitive to measure the effect of psychological interventions than general EQ-VAS.[27] At 36-month follow-up, these positive effects were no longer present. 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 dementia.[6,10] Most trials had short follow-up period, usually three to six months. One trial showed that a three-month programme of intensive physical exercise for the patients combined with teaching caregivers strategies to manage patients' behavioural problems improved the patients' physical functioning and depressive symptoms.[28] At 24-month follow-up, the improvement in physical functioning was still significant, but the improvement of depressive symptoms was no longer present.[28] In contrast, another trial with eight-year follow-up reported delayed nursing home placement for patients by providing a multicomponent interventions for the caregivers and patients; the ten-day intervention program was followed by continuous support over the telephone weekly for the first year and yearly thereafter for the next seven years.[29]

In our study, there are some possible explanations for the non-significant positive effects found at 12-month concerning patients' depressive symptoms and quality of life and the

disappearance of these effects at 36-month follow-up. First, it could be a floor effect. Our patients had minimal depressive symptoms and relatively high scores of QoL-AD at baseline. A randomised controlled trial using support group intervention for community-dwelling patients with mild Alzheimer's disease and their caregivers showed that patients who experienced improvement in their depressive symptoms had significantly more depressive symptoms at baseline and higher level of distress.[30] Second, there was no need assessment at baseline. Probably, participants with more symptoms and at greater need should have received the full intensive intervention programme and regular support follow-up was sufficient for those who had minimal symptoms and needs at baseline. Third, the control group also received some intervention that is much better than the usual practice in Denmark.[31] They had regular follow-ups when they could speak about emerging psychosocial and health problems, receive information about available resources, and get referred to relevant health professionals if needed. It is noteworthy that despite the marked decline in patients' global cognitive function, quality of life, and ADL between 12- and 36-month follow-ups, participants in both group had minimal changes in mean Cornell Depression Scale scores compared to baseline. This could be an indication that the regular follow-ups offered in this study were sufficient enough to produce a long-term effect in preventing the conversion into clinical depression for the patients. Fourth, as mentioned above, the intervention should probably continue longitudinally following the clinical progression in these patients to show long-term positive effects. The study did not find any long-term effect on DAISY intervention on the caregiver outcomes. Previous studies have shown positive responses to interventions from caregivers with high levels of depression and anxiety at baseline.[10] For this mostly asymptomatic group of caregivers in our study, perhaps follow-up at regular intervals provided enough information and support to prevent the emergence of depressive symptoms and maintain good life quality.

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

The same patient characteristics in the DAISY intervention group stated above could also explain the lack of effect concerning nursing home placement.[34] Additionally, continuous intervention and follow-up between 12 and 36 months could have been needed to produce a positive long-term effect on nursing home placement. Randomised controlled trials that reported positive long-term effect of psychosocial intervention on patients' nursing home placement provided continuous support and counselling over the phone for eight-nine years.[29,35] In contrast, intervention

lasting two years but without continuous follow-up and support showed no long-term effect on nursing home placement.[33]

Although this study found no long-term effect of DAISY intervention, a qualitative study linked to this randomised controlled trial showed that 80% of patients and 94% of caregivers in the intervention group found the intervention overall beneficial. Patients felt that their self-esteem was improved and they could better manage their daily life and social relations. Caregivers felt that they were more confident and competent to cope with the challenges of caring for relatives with AD. After the intervention, both patients and caregivers looked for support groups to join permanently and caregivers sought continuing counseling.[36] In contrast to randomised clinical trials about pharmacological interventions, we did not carry out the DAISY study to justify the reason for providing psychosocial intervention for patients with dementia and their caregivers, whose needs for information, counselling, and support cannot be denied. What we can conclude from this study is that since we could not show positive effects in the quantitative analyses, we should not offer psychosocial intervention indiscriminately to all patients with very mild dementia and their caregivers, but we should probably assess their needs and offer intervention only to those who need. Regular follow-up is therefore important to identify the arising needs that require intervention. Probably, the type, dose and intensity, and duration of early intervention should be more tailored to match the needs of patients and their caregivers at baseline to maximize benefit, economize resources, and avoid unnecessary intervention burden. The intervention program should perhaps be designed so that patients and caregivers with greater needs at baseline receive more intensive interventions that cater to their specific needs, those with lesser needs receive a basic intervention program of lower intensity, and those with minimal or no needs receive no intervention at all. To obtain long-term effect, early intervention should probably have a longitudinal and fluid course that

follows the disease progression, being continuously modified according to the needs that arise. These are the questions to be answered in future studies.

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Contributorship Statement

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

Data sharing

The dataset is available upon request to Gunhild Waldemar (Gunhild.waldemar@rh.regionh.dk)

References

1. Waldemar G, Waldorff FB, Buss DV, et al. The Danish Alzheimer intervention study: rationale, study design and baseline characteristics of the cohort. Neuroepidemiology. 2011;**36**:52-61.

2. Schulz R, Martire LM. Family caregiving of persons with dementia: prevalence, health effects, and support strategies. Am J Geriatr Psychiatry. 2004;**12**:240-9. Review.

3. van der Roest HG, Meiland FJ, Maroccini R, et al. Subjective needs of people with dementia: a review of the literature. Int Psychogeriatr. 2007;**19**:559-92.

4. Gaugler JE, Kane RL, Kane RA, et al. Unmet care needs and key outcomes in dementia J Am Geriatr Soc. 2005;**53**:2098-105.

5. Brodaty H, Green A, Koschera A. Meta-analysis of psychosocial interventions for caregivers of people with dementia. J Am Geriatr Soc 2003;**51**:657-64.

6. Brodaty H, Arasaratnam C. Meta-analysis of nonpharmacological interventions for neuropsychiatric symptoms of dementia. Am J Psychiatry. 2012;**169**:946-53.

7. Pinquart M, Sorensen S. Helping caregivers of persons with dementia: which interventions work and how large are their effects? Int Psychogeriatr 2006;**18**:577-95.

8. Thompson CA, Spilsbury K, Hall J, et al. Systematic review of information and support interventions for caregivers of people with dementia. BMC Geriatr 2007;7:18.

9. Schoenmakers B, Buntinx F, DeLepeleire J. Supporting the dementia family caregiver: the effect of home care intervention on general well-being. Aging Ment Health. 2010;**14**:44-56. Review.

10. Olazarán J, Reisberg B, Clare L, et al. Nonpharmacological therapies in Alzheimer's disease: a systematic review of efficacy. Dement Geriatr Cogn Disord. 2010;**30**:161-78.

11. Waldorf FB, Buss DV, Eckermann A, et al. Efficacy of psychosocial intervention in patients with mild Alzheimer's disease: the multicentre, rater blinded, randomised Danish Alzheimer Intervention Study (DAISY). BMJ Published Online First: 17 July 2012. doi: 10.1136/bmj.e4693.

12. Mittelman MS. The DAISY psychosocial intervention does not improve outcomes in patients with mild Alzheimer's disease or their carers. Evid Based Ment Health. 2013 Feb;**16**:15.

13. Folstein MF, Folstein SE, McHugh PR. "Mini-mental State". J Psychiat Res 1975;**12**:189-198.

14. American Psychiatric Association (APA). Diagnostic and Statistical Manual of Mental Disorders. DSM-IV, 4th edition. Washington, D.C., American Psychiatric Association, 1993

15. McKhann G, Drachman D, Folstein M, et al. Clinial diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984;**34:**939-944.

16. McKeith IG, Galasko D, Kosaka K, et al. Consensus guidelines for the clinical and pathological diagnosis of dementia with Lewy bodies (DLB): Report of the consortium on DLB international workshop. Neurology 1996;**47**:1113-1124.

17. Peavey VR. Sociodynamic Counseling: A Constructivist Perspective for the Practice of counselling in the 21st Century. Victoria. Trafford Publishing: 1997.

18. Alexopoulos GS, Abrams RC, Young RC, et al. Cornell scale for depression in dementia. Biol Psychiatry 1988;23:271-84.

19. The EuroQoL Group. EuroQoL-a new facility for the measurement of health-related quality of life. Health Policy 1990;**1**:199-208.

20. Yesavage JA, Brink TL, Rose TL, et al. Development and validation of a geriatric depression screening scale: a preliminary report. J Psychiatr Res 1982;**17**:37-49.

21. Logsdon RG, Gibbons LE, McCurry S, et al. Quality of life in Alzheimer's disease: patient and caregiver report (QoL-AD). J Ment Health Aging 1999;**5**:21-32.

22. Kaufer DI, Cummings JL, Ketchel P, et al. Validation of the NPI-Q, a brief clinical form of the neuropsychiatric inventory. J Neuropsychiatry Neurosci 2000;**12**:233-239.

23. Galasko D, Bennett D, Sano M, et al. An inventory to assess activities of daily living for clinical trials in Alzheimer's disease. The Alzheimer's Disease Cooperative Study. Alzheimer Dis Ass Dis 1997;**11(Suppl.2)**:S33-S39.

24. Pedersen CB, Gøtzsche H, Møller JØ, et al. The Danish Civil Registration System. Dan Med Bull 2006;**53**:441-449.

25. Dufouil C, Brayne C, Clayton D. Analysis of longitudinal studies with death and drop-out: a case study. Statistics in Medicine 2004;**23**:2215-2226.

26. Verhey FR, Houx P, Van Lang N, et al. Cross-national comparison and validation of the Alzheimer's Disease Assessment Scale: results from the European Harmonization Project for Instruments in Dementia (EURO-HARPID). Int J Geriatr Psychiatry. 2004;**19**:41-50.

27. Moniz-Cook E, Vernooij-Dassen M, Woods R, et al; INTERDEM group. A European consensus on outcome measures for psychosocial intervention research in dementia care. Aging Ment Health. 2008;**12**:14-29.

28. Teri, L., Gibbons, L.E., McCurry, et al. Exercise plus behavioral management in patients with Alzheimer disease: a randomized controlled trial. JAMA 2003;**290**:2015–2022.

29. Brodaty, H., Gresham,M., Luscombe, G. The Prince Henry Hospital dementia caregivers' training programme. Int. J. Geriatr. Psychiatry 1997;**12:**183–192.

30. Logsdon RG, Pike KC, McCurry SM, et al. Early-stage memory loss support groups: outcomes from a randomized controlled clinical trial. J Gerontol B Psychol Sci Soc Sci. 2010;**65**:691-7.

31. Phung TK, Andersen BB, Kessing LV, et al. Diagnostic evaluation of dementia in the secondary health care sector. Dement Geriatr Cogn Disord 2009;**27**:534-542.

32. Lund R, Due P, Modvig J, et al. Cohabitation and marital status as predictors of mortality--an eight year follow-up study. Soc Sci Med. 2002;**55**:673-9.

33. Brodaty H, Mittelman M, Gibson L, et al. The effects of counselling spouse caregivers of people with Alzheimer disease taking donepezil and of country of residence on rates of admission to nursing homes and mortality. Am J Geriatr Psychiatry. 2009;**17**:734-43.

34. Wattmo C, Wallin AK, Londos E, et al. Risk factors for nursing home placement in Alzheimer's disease: a longitudinal study of cognition, ADL, service utilization, and cholinesterase inhibitor treatment. Gerontologist. 2011;**51:**17-27.

35. Mittelman MS, Haley WE, Clay OJ, et al. Improving caregiver well-being delays nursing home placement of patients with Alzheimer disease. Neurology. 2006;**67**:1592-9.

36. Sørensen LV, Waldorff FB, Waldemar G. Early counselling and support for patient with mild Alzheimer's disease and their caregivers. A qualitative study on outcome. Aging Ment Health 2008;**12**:444-450.

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.

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.

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

Phung K [1], Waldorff FB[1,2], Buss DV[1], Eckermann A[1], Keiding N[3], Rishøj S[1], Siersma V[2], Sørensen J[4], Søgaard R[4], Sørensen LV[1], Vogel A[1], Waldemar G[1]

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

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Keywords : Randomised controlled trial, psychosocial, intervention study, dementia, caregivers

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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.~~

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

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

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 responsibly 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] Before adjustment for multiple testing was carried out, the data analysis of the results a~~A~~t 12-month follow-up~~,~~ had shown ~~there were indeed~~ statistical significance in ~~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~~ outcomes. 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

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

Intervention

A multifaceted and semi-tailored psychosocial intervention programme, described in details in our previous resports,[1,11] was designed to provide counselling, information, and support to patients with mild dementia and their caregivers in the intervention group. The study coordinator in each centre, an experienced nurse specialising in caring for patients with dementia and having received special training in counselling for the study (constructivist approach),[17] implemented the intervention within the first month after inclusion in the trial. Consisting of five key components, the intervention focused on positive resources, intact function, retained skills, and feasible activities for the patients: 1) The study coordinator provided seven individual counselling sessions tailored to the needs of the patients and their caregivers: two for the patient alone, two for the caregiver alone, two for the patient-caregiver dyad, and one with the dyad together with their family network (optional); 2) The study coordinator provided outreach telephone counselling 5-8 times with 3-4 week intervals to maintain regular contact and follow up on the individual counselling sessions; 3) Using log books, the patients and their caregivers independently kept track of the thoughts and daily issues that they wanted to discuss at the counselling sessions; 4) Experts in the field of dementia were invited to teach five standard courses as group intervention with separate courses for patients

and caregivers to provide general information about dementia and forum for discussion, sharing information, and support; 5) Patients and caregivers were provided with information folders produced especially for the purpose of the study about dementia causes, diagnosis and treatment, legal issues, and resources for social support. The intervention program lasted 8 to 12 months. Full compliance was defined as adherence with the major components of the intervention program: Patients who participated with their caregivers in at least 3 counselling sessions (not including the optional network session) and in at least 3 teaching course sessions.

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

Outcomes

Primary outcomes for the patients:

1. Global cognitive function: The patient's global cognitive function was assessed using Mini Mental State Examination (MMSE).[13] The sum of scores ranges from 0 to 30. Higher scores indicate better cognitive function.

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 System[24] 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 $\chi 2$ tests for categorical variables. With linear models on the full data of up to four observations per dyad, we

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

RESULTS

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

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

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

As reported previously, the 12-month follow-up study observed positive ~~trends~~ effects ~~concerning the effect~~ of DAISY intervention on preventing the emergence of depressive symptoms (Cornell depression scale, primary patient outcome) and maintaining quality of life (proxy-rated QoL-AD, secondary patient outcome).[11] The effect size of DAISY intervention regarding Cornell depression score 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 = 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 ~~in~~ 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.

To our knowledge, this study 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. A-priori sample size calculation was done. The measures for primary and secondary outcomes are reliable scales, which are commonly used in routine clinical practice and in intervention studies across cultures.[26,27] Proper randomisation, allocation concealment, rater-blinded evaluation of outcomes, and adjustment for multiple testing were rigorously carried out to reduce biases that could lead to type I errors.[11] 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.[2,5,7] Since ours was one of the first studies to examine the effect of support and counselling programmes in patients with very mild dementia, no previous consensus exists concerning gold standards for assessing efficacy. Therefore, multiple primary and secondary outcomes were exploratively chosen based on the specific aims of the DAISY intervention and on the outcomes from similar intervention studies for patients with more advanced dementia.[1] Consequently, to

avoid finding spurious effects, a significance level was set at P = 0.0005, which was subsequently criticized for being too conservative.[12] All patients in this study had primary caregivers who were very involved in caregiving, a situation that cannot be generalised to all patients with dementia in Denmark.

Although not statistically significant for this adjusted P value, DAISY intervention did produce small positive effects ~~trends~~ on reducing depressive symptoms ~~(Cornell depression score, P=0.0103)~~ and maintaining quality of life for the patients ~~(proxy rated QoL-AD, P=0.0013)~~ at 12-month follow-up.[11] The effect size of DAISY intervention regarding Cornell depression score 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 = 0.0013). The disease-specific QoL-AD is probably more sensitive to measure the effect of psychological interventions than general EQ-VAS.[27] At 36-month follow-up, these positive ~~trends~~ effects were no longer present. ~~(Cornell depression score, P = 0.93; proxy rated QoL-AD, P = 0.82).~~ 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 dementia.[6,10] Most trials had short follow-up period, usually three to six months. One trial showed that a three-month programme of intensive physical exercise for the patients combined

with teaching caregivers strategies to manage patients' behavioural problems improved the patients' physical functioning and depressive symptoms.[28] At 24-month follow-up, the improvement in physical functioning was still significant, but the improvement of depressive symptoms was no longer present.[28] In contrast, another trial with eight-year follow-up reported delayed nursing home placement for patients by providing a multicomponent interventions for the caregivers and patients; the ten-day intervention program was followed by continuous support over the telephone weekly for the first year and yearly thereafter for the next seven years.[29]

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

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

It is not known why ~~P~~patients in the intervention group had higher mortality than those in the control group. This increased mortality was unlikely to be caused by the intervention, as the nature of the intervention program did not subject the patients to any health risk. Using the data from Statistics Denmark (www.dst.dk), the incidence of death for the age-matched general population over the same time period was found to be similar to that of the DAISY intervention group. The control group however had lower incidence of death compared to the general population. At baseline, the quality of life of the patients in the intervention group was rated as poorer than that of the control group, both by the patients themselves and by their caregivers (Table 1). Although not statistically significant, there were small socioeconomic and clinical differences that ~~were in favour of the control group~~ could be responsible for the higher mortality rate in the intervention groups. More patients in the intervention group lived alone (4% difference), rented their house (7% difference), had more co-morbidities (4.4% difference), and were diagnosed with mixed AD and vascular dementia (4.2% difference, Table 1). Whether these differences could contribute to the higher mortality in the intervention group is uncertain. It is known that older people living alone have higher mortality than those living with others.[32] Currently, there is

insufficient evidence in the literature concerning the effect of psychosocial intervention on patient mortality, as studies looking at this effect are scarce.[5,33]

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

Although this study found no long-term effect of DAISY intervention, a qualitative study linked to this randomised controlled trial showed that ~~promising indications that early psychosocial intervention for patient with very mild Alzheimer's disease and their caregivers could potentially prevent the emergence of depressive symptoms and maintain the quality of life for the patients.[36] This study revealed that both patients and caregivers found the DAISY intervention stimulating and rewarding.~~ 80% of patients and 94% of caregivers in the intervention group found the intervention overall beneficial. Patients felt that their self-esteem was improved and they could better manage their daily life and social relations. Caregivers felt that they were more confident and competent to cope with the challenges of caring for relatives with AD. After the intervention, both patients and caregivers looked for support groups to join permanently and caregivers sought continuing counseling.[36] In contrast to randomised clinical trials about pharmacological interventions, we did not carry out the DAISY study to justify the reason for providing psychosocial intervention for patients with dementia and their caregivers, whose needs for information, counselling, and support cannot be denied. What we can conclude from this study is that since we

could not show positive effects in the quantitative analyses, we should not offer psychosocial intervention indiscriminately to all patients with very mild dementia and their caregivers, but we should probably assess their needs and offer intervention only to those who need. Regular follow-up is therefore important to identify the arising needs that require intervention. Probably, ~~The lessons learned from this study is that~~ the typecontent, dose and intensity, and duration of early intervention shouldcan be more tailored to match the needs of patients and their caregivers at baseline to maximize benefit, economize resources, and avoid unnecessary intervention burden. ~~Need assessment is of primary importance.~~ The intervention program should perhaps be designed so that patients and caregivers with greater needs at baseline receive more intensive interventions that cater to their specific needs, those with lesser needs receive a basic intervention program of lower intensity, and those with minimal or no needs receive no intervention at all. ~~Regular follow-up assessment is necessary to identify emerging needs.~~ To obtain long-term effect, early intervention should probably have a longitudinal and fluid course that follows the disease progression, being continuously modified according to the needs that arise. These are the questions to be answered in future studies.

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References

1. Waldemar G, Waldorff FB, Buss DV, et al. The Danish Alzheimer intervention study: rationale, study design and baseline characteristics of the cohort. Neuroepidemiology. 2011;**36**:52-61.

2. Schulz R, Martire LM. Family caregiving of persons with dementia: prevalence, health effects, and support strategies. Am J Geriatr Psychiatry. 2004;**12**:240-9. Review.

3. van der Roest HG, Meiland FJ, Maroccini R, et al. Subjective needs of people with dementia: a review of the literature. Int Psychogeriatr. 2007;**19**:559-92.

4. Gaugler JE, Kane RL, Kane RA, et al. Unmet care needs and key outcomes in dementia J Am Geriatr Soc. 2005;**53**:2098-105.

5. Brodaty H, Green A, Koschera A. Meta-analysis of psychosocial interventions for caregivers of people with dementia. J Am Geriatr Soc 2003;**51**:657-64.

6. Brodaty H, Arasaratnam C. Meta-analysis of nonpharmacological interventions for neuropsychiatric symptoms of dementia. Am J Psychiatry. 2012;**169**:946-53.

7. Pinquart M, Sorensen S. Helping caregivers of persons with dementia: which interventions work and how large are their effects? Int Psychogeriatr 2006;**18**:577-95.

8. Thompson CA, Spilsbury K, Hall J, et al. Systematic review of information and support interventions for caregivers of people with dementia. BMC Geriatr 2007;7:18.

9. Schoenmakers B, Buntinx F, DeLepeleire J. Supporting the dementia family caregiver: the effect of home care intervention on general well-being. Aging Ment Health. 2010;**14**:44-56. Review.

10. Olazarán J, Reisberg B, Clare L, et al. Nonpharmacological therapies in Alzheimer's disease: a systematic review of efficacy. Dement Geriatr Cogn Disord. 2010;**30**:161-78.

11. Waldorf FB, Buss DV, Eckermann A, et al. Efficacy of psychosocial intervention in patients with mild Alzheimer's disease: the multicentre, rater blinded, randomised Danish Alzheimer Intervention Study (DAISY). BMJ Published Online First: 17 July 2012. doi: 10.1136/bmj.e4693.

12. Mittelman MS. The DAISY psychosocial intervention does not improve outcomes in patients with mild Alzheimer's disease or their carers. Evid Based Ment Health. 2013 Feb;**16**:15.

13. Folstein MF, Folstein SE, McHugh PR. "Mini-mental State". J Psychiat Res 1975;**12**:189-198.

14. American Psychiatric Association (APA). Diagnostic and Statistical Manual of Mental Disorders. DSM-IV, 4th edition. Washington, D.C., American Psychiatric Association, 1993

15. McKhann G, Drachman D, Folstein M, et al. Clinial diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984;**34:**939-944.

16. McKeith IG, Galasko D, Kosaka K, et al. Consensus guidelines for the clinical and pathological diagnosis of dementia with Lewy bodies (DLB): Report of the consortium on DLB international workshop. Neurology 1996;**47**:1113-1124.

17. Peavey VR. Sociodynamic Counseling: A Constructivist Perspective for the Practice of counselling in the 21st Century. Victoria. Trafford Publishing: 1997.

18. Alexopoulos GS, Abrams RC, Young RC, et al. Cornell scale for depression in dementia. Biol Psychiatry 1988;23:271-84.

19. The EuroQoL Group. EuroQoL-a new facility for the measurement of health-related quality of life. Health Policy 1990;**1**:199-208.

20. Yesavage JA, Brink TL, Rose TL, Lum O, Huang V, Adey M, et al. Development and validation of a geriatric depression screening scale: a preliminary report. J Psychiatr Res 1982;**17**:37-49.

21. Logsdon RG, Gibbons LE, McCurry S, Teri L. Quality of life in Alzheimer's disease: patient and caregiver report (QoL-AD). J Ment Health Aging 1999;**5**:21-32.

22. Kaufer DI, Cummings JL, Ketchel P, et al. Validation of the NPI-Q, a brief clinical form of the neuropsychiatric inventory. J Neuropsychiatry Neurosci 2000;**12**:233-239.

23. Galasko D, Bennett D, Sano M, et al. An inventory to assess activities of daily living for clinical trials in Alzheimer's disease. The Alzheimer's Disease Cooperative Study. Alzheimer Dis Ass Dis 1997;**11(Suppl.2)**:S33-S39.

24. Pedersen CB, Gøtzsche H, Møller JØ, et al. The Danish Civil Registration System. Dan Med Bull 2006;**53**:441-449.

25. Dufouil C, Brayne C, Clayton D. Analysis of longitudinal studies with death and drop-out: a case study. Statistics in Medicine 2004;**23**:2215-2226.

26. Verhey FR, Houx P, Van Lang N, et al. Cross-national comparison and validation of the Alzheimer's Disease Assessment Scale: results from the European Harmonization Project for Instruments in Dementia (EURO-HARPID). Int J Geriatr Psychiatry. 2004;**19**:41-50.

27. Moniz-Cook E, Vernooij-Dassen M, Woods R, et al; INTERDEM group. A European consensus on outcome measures for psychosocial intervention research in dementia care. Aging Ment Health. 2008;**12**:14-29.

28. Teri, L., Gibbons, L.E., McCurry, et al. Exercise plus behavioral management in patients with Alzheimer disease: a randomized controlled trial. JAMA 2003;**290**:2015–2022.

29. Brodaty, H., Gresham,M., Luscombe, G. The Prince Henry Hospital dementia caregivers' training programme. Int. J. Geriatr. Psychiatry 1997;**12:**183–192.

30. Logsdon RG, Pike KC, McCurry SM, et al. Early-stage memory loss support groups: outcomes from a randomized controlled clinical trial. J Gerontol B Psychol Sci Soc Sci. 2010;**65**:691-7.

31. Phung TK, Andersen BB, Kessing LV, et al. Diagnostic evaluation of dementia in the secondary health care sector. Dement Geriatr Cogn Disord 2009;**27**:534-542.

32. Lund R, Due P, Modvig J, et al. Cohabitation and marital status as predictors of mortality--an eight year follow-up study. Soc Sci Med. 2002;**55**:673-9.

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33. Brodaty H, Mittelman M, Gibson L, et al. The effects of counselling spouse caregivers of people with Alzheimer disease taking donepezil and of country of residence on rates of admission to nursing homes and mortality. Am J Geriatr Psychiatry. 2009;**17**:734-43.

34. Wattmo C, Wallin AK, Londos E, et al. Risk factors for nursing home placement in Alzheimer's disease: a longitudinal study of cognition, ADL, service utilization, and cholinesterase inhibitor treatment. Gerontologist. 2011;**51:**17-27.

35. Mittelman MS, Haley WE, Clay OJ, et al. Improving caregiver well-being delays nursing home placement of patients with Alzheimer disease. Neurology. 2006;**67**:1592-9.

36. Sørensen LV, Waldorff FB, Waldemar G. Early counselling and support for patient with mild Alzheimer's disease and their caregivers. A qualitative study on outcome. Aging Ment Health 2008;**12**:444-450.

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.

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.

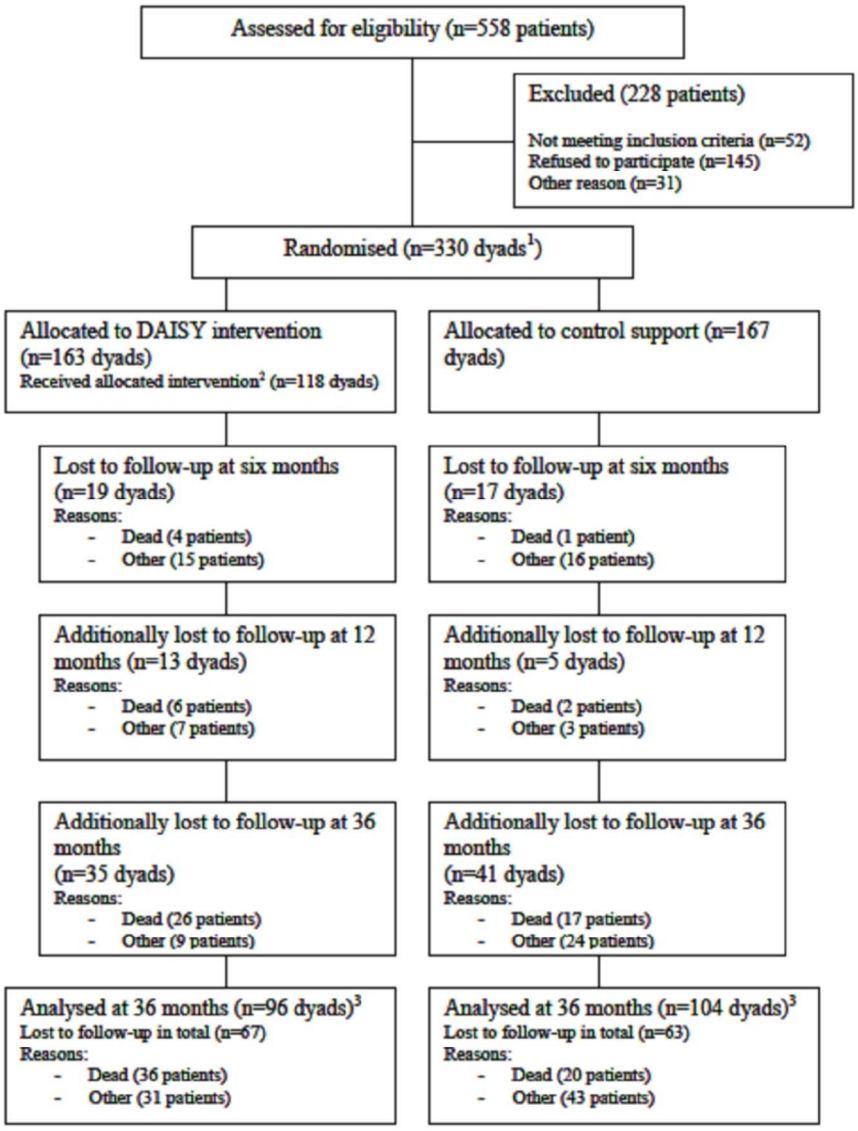

Figure 1: Trial flow for Danish Alzheimer Intervention Study (DAISY)
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Table 2 (alternative): Outcome of DAISY psychosocial interventions based on completed response at 36-month follow-up. All analyses were intention-to-treat.

	Observed scores		Change from baseline		Differences in scores, intervention versus control*	
	Intervention	Control	Intervention	Control		
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (95%CI)	P-value
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

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

*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.