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RESEARCH ARTICLE

Determinants of informal care time, distress, depression, and quality of life in care partners along the trajectory of Alzheimer's disease

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Abstract

Introduction: We evaluated determinants associated with care partner outcomes along the Alzheimer's disease (AD) stages.

Methods: We included $n = 270$ care partners of amyloid-positive patients in the pre-dementia and dementia stages of AD. Using linear regression analysis, we examined determinants of four care partner outcomes: informal care time, caregiver distress, depression, and quality of life (QoL).

Results: More behavioral symptoms and functional impairment in patients were associated with more informal care time and depressive symptoms in care partners. More behavioral symptoms were related with more caregiver distress. Spouse care partners spent more time on informal care and QoL was lower in female care partners. Behavioral problems and subtle functional impairment of the patient predisposed for worse care partner outcomes already in the pre-dementia stages.

Discussion: Both patient and care partner determinants contribute to the care partner outcomes, already in early disease stages. This study provides red flags for high care partner burden.

KEYWORDS
Alzheimer's disease, caregiver, dementia, depression, informal care time, mild cognitive impairment, subjective cognitive decline, quality of life

1 | INTRODUCTION

Alzheimer's disease (AD) is a gradually progressive, neurodegenerative disorder with a long pre-dementia stage, that ultimately leads to dementia.[1] Pre-dementia stages include mild cognitive impairment (MCI) and preclinical AD, which sometimes manifests as subjective cognitive decline (SCD). Biomarkers enable the diagnosis of AD in pre-dementia stages.[2] Studies on care partner outcomes in the pre-dementia stages of AD are scarce, yet may inform health-care policy makers and identify touch points for organizing care. Clinically, AD is characterized by gradually increasing cognitive impairment and functional dependency and behavioral problems, necessitating increasing levels of support.[3] It is unknown to what extent each of these symptom groups contribute to care partner burden along the disease trajectory.

Care partners play an important role in health care by supporting with daily activities, a role that becomes more important today as the prevalence of AD is increasing worldwide, and the work force declines in size. Care partners of patients with dementia often feel burdened and overworked.[3,4] Previous studies have shown that both patient characteristics and care partner factors are associated with more care partner burden in the dementia stage, such as a younger care partner age,[5,6] care partner female sex,[6,7] spousal relationship,[8] increasing AD severity,[6,7,9] decreased functional ability of the patient,[5,6,8] higher levels of care partner distress due to patient behavior,[5,6] more hours of caregiving,[7–9] and care partner self-reported depression.[5]

A high care partner burden affects the physical and mental health of the care partners, including a higher risk of depression, care partner distress due to patient behavioral problems, and a lower quality of life, which in turn results in higher health-care costs.[10–13] However, even though the disease trajectory starts well before the dementia stage, there are no studies on these outcomes available in the pre-dementia stage of AD.[13–16] Furthermore, biomarker support of diagnosis is lacking in most studies, rendering unclear whether findings are specific for AD. In addition, review studies have highlighted the need to further examine the factors that contribute to depression and quality of life in care partners of those with AD, as insight into these factors helps inform the development of support services that help care partners maintain a good quality of life and manage the emotional demands of caring for an AD patient.[17–19] Therefore, the aim of this study is to determine whether informal care time, caregiver distress, depression, and quality of life (QoL) in care partners of amyloid-positive patients are associated with patient and care partner determinants.

2 | METHODS

2.1 | Participants and data collection

In this study, we included $n = 270$ care partners of amyloid-positive patients from the Amsterdam Dementia Cohort (ADC).[20] ADC is a prospective memory clinic–based cohort in which all patients received a standardized dementia diagnostic work-up, which consisted of medical history; neurological, physical, and neuropsychological evaluation; brain magnetic resonance imaging (MRI); laboratory tests; and assessment of AD biomarkers by lumbar puncture or amyloid-positron emission tomography (PET).[20,21] In addition, patients were invited for an annual follow-up visit including clinical assessment and neuropsychological evaluation.[20,21] In 2020, we started onlineADC; an online data collection of questionnaires of patient reported outcomes.[22] We invited patients who had ever visited the memory clinic and their care partners by e-mail to complete the questionnaires in onlineADC.

Patients visited the memory clinic between 2009 and 2020. Based on information from their last available visit at which diagnosis was established (last observation carried forward), we included care partners of $n = 28$ patients with SCD, $n = 38$ with MCI, and $n = 204$ with AD dementia. Participants were included when (1) they were care partners of patients with a amyloid-positive diagnosis of AD dementia, MCI, or SCD, as supported by an amyloid-positive PET and/or cerebrospinal fluid (CSF) biomarkers, and (2) data was available on care partner outcomes. The study was approved by the medical ethics review committee of the Vrije Universiteit University Medical Center. All patients and care partners provided written informed consent for the use of their medical data for research purposes.

2.2 | Patient data

2.2.1 | Diagnosis of amyloid-positive SCD, MCI, and dementia

Clinical diagnosis was determined in a multi-disciplinary meeting. Patients were diagnosed with AD dementia or MCI according to the National Institute on Aging–Alzheimer's Association diagnostic

framework.[2,23–25] Patients were labeled SCD when they presented with cognitive complaints; had normal clinical and cognitive test results; and did not meet the criteria for MCI, dementia, or other neurologic or psychiatric conditions.[26]

We included only patients who were categorized as amyloid-positive, based on a positive amyloid-PET scan (n = 47) or abnormal CSF amyloid beta ($Aß_{1-42}$ values (n = 223). Amyloid-PET scans were made using 3-Tesla Ingenuity TF PET/MRI, Ingenuity TF PET/computed tomography (CT), or Gemini TF PET/CT scanners (Philips Healthcare). Scans were visually rated by an experienced nuclear medicine physician. The amyloid-PET using ^{18}F-florbetaben (n = 22), ^{18}F-fFlorbetapir (n = 5), ^{18}F-flutemetamol (n = 10), or ^{11}C-Pittsburgh compound B (n = 10) have been described in detail elsewhere.[27,28] CSF was obtained by lumbar puncture, collected in polypropylene tubes (Sarstedt), and processed according to international guidelines.[29] Before 2018, amyloid beta, total tau, and phosphorylated threonine 181 were measured using sandwich enzyme-linked immunosorbent assays (ELISAs; Innotest, Fujirebio).[30] Aß values were drift-corrected.[31] After 2018, CSF was analyzed using Elecsys (Roche). CSF concentrations were considered amyloid-positive if CSF $Aß_{1-42}$ drift-corrected ELISA <813 or CSF $Aß_{1-42}$ Elecsys <1000 pg/ml.

2.2.2 | Patient determinants

The patient determinants included patient's age, severity of AD symptoms (i.e., cognitive [dementia status and Mini-Mental State Examination (MMSE)], functional [Instrumental Activities of Daily Living (IADL)], behavioral [Neuropsychiatric Inventory-Questionnaire (NPI-Q severity)]), and comorbidity (Charlson Comorbidity Index [CCI]) of the patient.

The following patient determinants were collected based on information from their last available visit at which diagnosis was established: dementia status (i.e., SCD/MCI or AD dementia), CCI, and MMSE.[32,33] CCI was calculated based on medical history and medication use (CCI score ranges from 0 [no comorbidity] to 37 [high comorbidity]). The median (interquartile range [IQR]) time between the last available AD stage diagnosis of the patient at the memory clinic and completing the onlineADC questionnaires was 2 (1–4) years.

In onlineADC, care partners completed the NPI-Q and Amsterdam IADL. NPI-Q is a shorter version of the NPI, which assesses severity of the neuropsychiatric symptoms of the patient. NPI-Q severity score ranges from 1 (not severe) to 36 (very severe).[34] The Amsterdam IADL questionnaire consists of 29 items, measuring the functional ability of the patient. We calculated total scores using item response theory (IRT). This scoring method is described in more detail elsewhere.[35,36]

2.3 | Care partner data

All care partner data were obtained from onlineADC questionnaires, completed by the care partner.

RESEARCH IN CONTEXT

1. **Systematic Review**: We reviewed the literature using traditional sources (e.g. Pubmed). Extending on previous studies on care partners in dementia due to Alzheimer's disease (AD), we included patients across the biomarker-confirmed dementia status of Subjective Cognitive Decline (SCD), Mild Cognitive Impairment (MCI) and dementia and we studied determinants associated with multiple care partner outcomes.
2. **Interpretation**: Both care partner characteristics and patient's symptoms contributed to detrimental care partner outcomes. Being a female care partner, having a spousal relationship, behavioral problems and functional impairment of the patient were associated with care partner burden. Behavioral problems and subtle functional impairment of the patient were already associated with care partner outcomes in the pre-dementia stages.
3. **Future directions**: This study helps to identify care partners at risk of high burden. Future studies should address how wellbeing of these high-risk care partners can be optimized.

2.3.1 | Care partner determinants

The following demographic care partner characteristics were obtained from the Resource Utilization in Dementia (RUD) Lite questionnaire: age, sex, and relation to the patient.[37]

2.3.2 | Care partner outcomes

The care partner outcomes included total informal care hours per day (RUD Lite), NPI-Q caregiver distress, depressive symptoms of care partners measured using Geriatric Depression Scale (GDS), and QoL of care partners measured using Visual Analogue Scale (VAS) and the European Quality of Life-5 Dimensions (EQ-5D).

RUD Lite was used to assess how much time care partners spend caring for the patient, at the time of completing the questionnaire.[37] Informal care hours per day was calculated as the sum of hours per day spent on IADL, activities of daily living (ADL), and supervision of the patient. If the sum of these activities exceeded 24 hours, we set the total number of informal hours to 24.

NPI-Q is a shorter version of the NPI, which assesses severity of the neuropsychiatric symptoms of the patient (i.e., NPI-Q severity; see patient determinants). In addition, care partners had to rate the level of the symptom's impact on themselves (i.e., caregiver distress).[34] The NPI-Q caregiver distress score was calculated as the sum of the caregiver distress rate of the 12 neuropsychiatric behavioral symptoms, ranging from 0 (no caregiver distress) to 60 (high caregiver distress).

The GDS measures presence of depressive symptoms in care partners.[38] This questionnaire contains 15 statements for which care partners had to answer "yes" or "no." We calculated a total score based on the 15 items, ranging from 0 (no depressive symptoms) to 15 (many depressive symptoms).

The EuroQoL Group developed a standardized, non–disease-specific instrument for describing and valuing health states and consists of two parts (i.e., EQ-5D-5L and VAS).[39] In the EQ-5D-5L (first part of the questionnaire), care partners were asked to rate their own current health state in terms of five domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ-5D-5L has five possible responses: no problems, slight problems, moderate problems, severe problems, or unable to/extreme problems. A summary index score (i.e., EQ-5D utility) can be calculated based on weights for each item, which differ between countries. The EQ-5D-5L responses of this study were converted into an EQ-5D utility using a Netherlands-based algorithm, provided by the EuroQoL Group.[40] The EQ-5D utility ranges from 1 (perfect health) to 0 (death), and has negative values indicating a health state worse than death. The VAS, the second part of the questionnaire, assesses the current health status, ranging from 0 (the worst health) to 100 (the best health).

2.4 | Statistical analysis

Descriptive analyses were performed using STATA SE version 14.0. To evaluate differences in patient determinants, care partner determinants, and care partner outcomes between AD dementia and pre-dementia groups we used analyses of variance for normally distributed continuous variables, Kruskal–Wallis tests for non-normally distributed continuous or ordinal variables, and chi-square tests for categorical variables. Because most patient determinants reflect AD severity, we estimated pairwise correlations between these variables (Table S1 in supporting information). We also estimated pairwise correlations between care partner outcome measures (Table S2 in supporting information).

We developed univariable and multivariable linear regression models to evaluate determinants (i.e., age, sex, MMSE, CCI, NPI-Q, and IADL of the patient; age, sex of the care partner; and spousal relationship) of care partner outcomes for all care partners (i.e., regardless of the dementia status of the patient). Then, we repeated the analyses stratified based on the dementia status of the patient (SCD/MCI vs. AD dementia).

In a sensitivity analysis, we repeated the analyses based on log transformations of the continuous care partner outcomes to reduce the skewness of some of the continuous care partner outcomes. In additional sensitivity analysis, we added interaction terms between time and dementia status, MMSE, and CCI to the models. Time between diagnosis assessment and completing the online questionnaires could be an effect modifier for dementia status, MMSE, and CCI, because we used last observation carried forward for dementia status, MMSE, and CCI, as these variables were only measured when patients visited the memory clinic.

3 | RESULTS

3.1 | Patient and care partner description

Description of the included patients and their care partners are summarized in Table 1. Of the patients, the mean (standard deviation [SD]) age was 67.3 (7.05) years, $n = 128$ (47%) were female, and median (IQR) MMSE was 24 (20; 27). Of the care partners, mean (SD) age was 65.2 (9.1) years, $n = 153$ (57%) were female, and most of the care partners were spouse ($n = 242$ [90%]).

3.2 | Care partner outcomes

The care partner outcomes of the total group and stratified by dementia status are shown in Table 2. Overall, the median informal care time was 3.0 (0.0; 10.0) hours per day, the NPI-Q caregiver distress score was 6.0 (0.0; 13.0), the GDS score was 2.0 (1.0; 4.0), EQ-5D was 0.89 (0.82; 1.0), and VAS was 85.5 (72; 94). In care partners of patients with SCD/MCI, the median informal care time was 0.0 (0.0; 2.0) hours per day, NPI-Q caregiver distress was 1.5 (0.0; 5.0), GDS was 1.0 (0.0; 3.0), EQ-5D was 0.86 (0.81; 1.0), and VAS was 86.5 (71; 93). In care partners of patients with dementia, the median informal care time was 4.0 (1.0; 13.5) hours per day, NPI-Q caregiver distress was 9.0 (3.0; 15.0), GDS score was 2.0 (1.0; 4.0), EQ-5D was 0.89 (0.83; 1.0), and VAS was 85.0 (74.0; 94.0). Boxplots of care partner outcomes by dementia status are shown in Figure S1 in supporting information.

First we considered the whole sample. Univariable analyses (Table 3) showed that the following patient determinants were associated with a higher number of informal care hours per day and more NPI-Q caregiver distress: diagnosis of dementia, lower MMSE, more behavior problems, and worse IADL functioning. Older age of the care partner and a spousal relationship were also associated with a higher number of informal care hours. The following patient determinants predetermined for more depressive symptoms in care partners: diagnosis of dementia, behavior symptoms, and worse IADL functioning. Being a female care partner was associated with a lower QoL, as measured with EQ-5D and VAS.

Subsequently, multivariable models confirmed that both patient and care partner determinants contributed to the care partner outcomes and showed that cognitive determinants (dementia status and MMSE) were no longer associated with care partner outcomes (Table 3). More behavioral symptoms (B[standard error (SE)] = 0.22 [0.08]) and worse IADL functioning (B[SE] = −0.21 [0.04]) in patients and a spousal relationship (B[SE] = 4.95 [1.78]) predisposed for more informal care hours per day. Higher NPI-Q severity was associated with higher NPI-Q caregiver distress (B[SE] = −0.20 [0.04]). More behavioral symptoms (B[SE] = 0.12 [0.03]) and worse IADL functioning (B[SE] = −0.04 [0.02]) in patients were related to a higher GDS score. Female care partners reported lower QoL (EQ-5D: B[SE] = −0.06 [0.02]; VAS: B[SE] = −5.25 [2.38]).

We also stratified the analysis for dementia status (SCD/MCI vs. AD dementia; Tables 4 and 5). Multivariate analysis in care partners

TABLE 1 Descriptive analyses of patients and their care partners.

	All participants ($n = 270$)	Patient's dementia status		
		SCD/MCI ($n = 66$)	Dementia ($n = 204$)	*P*-value
Patient description				
Age, mean years (SD)	67.3 (7.1)	67.7 (7.0)	67.3 (7.08)	0.68
Female, *n* (%)	128 (47)	26 (39)	102 (50)	0.13
MMSE, median (IQR)	24 (20; 27)	28 (25; 29)	23 (19; 25)	<0.001
CCI, mean (SD)	3.2 (1.2)	2.7 (1.3)	3.3 (1.2)	<0.001
NPI-Q severity, median (IQR)	5.0 (2.0; 10.0)	1.5 (0.0; 5.0)	6.0 (3.0; 12.0)	<0.001
Amsterdam IADL*, median (IQR)	37.6 (25.9; 51.7)	53.8 (48.8; 63.1)	32.4 (22.4; 41.8)	<0.001
Care partner description				
Age, mean years (SD)	65.2 (9.1)	65.0 (9.3)	65.2 (9.1)	0.60
Female, *n* (%)	153 (57)	110 (54)	153 (57)	0.11
Relation to patient: spouse, *n* (%)	242 (90)	181 (88)	242 (90)	0.39

*Calculated using item response theory (IRT).
Abbreviations: CCI, Charlson Comorbidity Index; GDS, Geriatric Depression Scale; IADL, Instrumental Activities of Daily Living; IQR, interquartile range; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; NPI-Q, Neuropsychiatric Inventory Questionnaire; SCD, subjective cognitive decline; SD, standard deviation.
Notes: *P*-values were obtained using independent samples *t* tests or analysis of variance for normally distributed continuous variables (mean [SD]), Mann-Whitney two sample tests for non-normally distributed continuous variables (median [IQR]), and chi-square tests for categorical variables (*n* [%]).

TABLE 2 Care partner outcomes in pre-dementia and dementia stages.

	All participants ($n = 270$)	Patient's dementia status		
		SCD/MCI ($n = 66$)	Dementia ($n = 204$)	*P*-value
Care partner outcomes				
Total informal care hours per day, median (IQR)	3 (0.0; 10.0)	0.0 (0.0; 2.0)	4.0 (1.0; 13.5)	<0.001
NPI-Q caregiver distress, median (IQR)	6.0 (1.0; 13.0)	1.5 (0.0; 5.0)	9.0 (3.0; 15.0)	<0.001
GDS, median (IQR)	2.0 (1.0; 4.0)	1.0 (0.0; 3.0)	2.0 (1.0; 4.0)	0.003
EQ-5D utility, median (IQR)	0.89 (0.82; 1.0)	0.86 (0.81; 1.0)	0.89 (0.83; 1.0)	0.25
VAS, median (IQR)	85.5 (72; 94)	86.5 (71; 93)	85.0 (74.0; 94.0)	0.77

Abbreviations: EQ-5D, the European Quality of Life-5 Dimensions; GDS, Geriatric Depression Scale; IQR, interquartile range; MCI, mild cognitive impairment; NPI-Q, Neuropsychiatric Inventory Questionnaire; SCD, subjective cognitive decline; VAS, Visual Analogue Scale.
Notes: *P*-values were obtained using independent samples *t* tests or analysis of variance for normally distributed continuous variables (mean [SD]), Mann-Whitney two sample tests for non-normally distributed continuous variables (median [IQR]), and chi-square tests for categorical variables (*n* [%]).

of patients with dementia showed that more behavioral symptoms and worse IADL functioning of the patient and a spousal relation were associated with more informal care time. In care partners of patients with SCD/MCI, only functional impairment of the patient was associated with informal care time, while associations with behavioral symptoms and a spousal relation were not significant. In both strata, behavioral symptoms and worse IADL functioning in patients were related to more NPI-Q caregiver distress. In care partners of patients with AD dementia, more behavioral problems and worse IADL functioning in patients were associated with more depressive symptoms as measured using GDS in care partners; we found no determinants of depressive symptoms in care partners of patients with SCD/MCI. In both strata, no determinants were associated with QoL (EQ-5D and VAS).

3.3 | Sensitivity analyses

The results of the univariable and multivariable analyses based on log transformations of the continuous care partner outcomes (Table S3 in supporting information) followed the same patterns as the main results presented in Table 3. Multivariable analyses showed that in addition to a spousal relationship, behavioral symptoms and functional impairment in the patient and disease severity in terms of dementia

TABLE 3 Univariable and multivariable linear regression models to evaluate determinants of care partner outcomes in all amyloid-positive participants.

	Informal care hours per day (RUD Lite)		Caregiver distress (NPI-Q)		Depression (GDS)		Quality of Life (EQ-5D)		Quality of Life (VAS)	
	Univariable	Multivariable	Univariable	Multivariable	Univariable	Multivariable	Univariable	Multivariable	Univariable	Multivariable
	B (SE)	*B* (SE)	*B* (SE)	*B* (SE)	*B* (SE)	*B* (SE)	*B* (SE)	*B* (SE)	*B* (SE)	*B* (SE)
Patient determinants										
Age	0.05 (0.07)	−0.01 (0.10)	0.05 (0.08)	−0.06 (0.05)	0.005 (0.03)	0.03 (0.04)	−0.002 (0.001)	−0.003 (0.002)	−0.29 (0.15)	−0.17 (0.26)
Dementia status: dementia	5.87 (1.11)[a]	1.57 (1.35)	1.18 (0.42)[a]	0.61 (0.65)	7.09 (1.19)[a]	0.29 (0.55)	0.04 (0.02)	0.03 (0.03)	0.69 (2.45)	1.18 (3.34)
MMSE	−0.41 (0.10)[†]	0.11 (0.12)	−0.53 (0.11)[a]	0.10 (0.06)	−0.06 (0.04)	0.04 (0.05)	−0.003(0.002)	−0.001 (0.003)	−0.15 (0.22)	−0.26 (0.29)
CCI	0.16 (0.40)	−0.19 (0.50)	0.52 (0.44)	0.33 (0.24)	−0.04 (0.15)	−0.13 (0.20)	0.001 (0.008)	0.01 (0.01)	−0.64 (0.85)	0.61 (1.22)
NPI-Q severity	0.47 (0.07)[a]	0.22 (0.08)[a]	1.25 (0.03)[a]	1.22 (0.04)[a]	0.15 (0.03)[a]	0.12 (0.03)[a]	−0.001 (0.001)	−0.003 (0.001)	−0.18 (0.16)	−0.19 (0.20)
Amsterdam IADL	−0.26 (0.03)[a]	−0.21 (0.04)[a]	−0.31 (0.03)[†]	−0.03 (0.02)	−0.06 (0.01)[a]	−0.04 (0.02)[*]	−0.0002 (0.0006)	0.0001 (0.001)	0.07 (0.07)	0.10 (0.11)
Care partner determinants										
Age	0.12 (0.05)[*]	0.06 (0.08)	−0.04 (0.06)	0.03 (0.04)	−0.006 (0.02)	−0.03 (0.03)	−0.001 (0.001)	−0.002 (0.002)	−0.19 (0.11)	−0.21 (0.19)
Sex, female	−0.34 (1.01)	0.46 (0.96)	0.70 (1.10)	0.18 (0.46)	0.72 (0.37)	0.68 (0.39)	−0.06 (0.02)[a]	−0.06 (0.02)[a]	−4.69 (2.10)[*]	−5.25 (2.38)[*]
Relation to patient, partner	4.87 (1.62)[a]	4.95 (1.78)[a]	−1.61 (1.79)	−0.01 (0.85)	0.80 (0.60)	1.41 (0.73)	−0.02 (0.03)	−0.003 (0.04)	−2.63 (3.45)	−0.40 (4.40)

[*] Significant based on $P < 0.05$.

[a] Significant based on $P < 0.01$.

Notes: Data are represented as beta coefficients (SE) and odds ratio (95% CI). Analyses were not corrected for multiple testing.

Abbreviations: CCI, Charlson Comorbidity Index; CI, confidence interval; EQ-5D, the European Quality of Life-5 Dimensions; GDS, Geriatric Depression Scale; IADL, Instrumental Activities of Daily Living; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; NPI-Q, Neuropsychiatric Inventory Questionnaire; RUD, Resource Utilization in Dementia; SCD, subjective cognitive decline; SE, standard error; VAS, Visual Analogue Scale.

TABLE 4 Univariable and multivariable linear regression models in SCD/MCI.

	Informal care hours per day		NPI-Q caregiver distress		GDS		EQ-5D		VAS	
	Univariable *B* (SE)	Multivariable *B* (SE)	Univariable *B* (SE)	Multivariable *B* (SE)	Univariable *B* (SE)	Multivariable *B* (SE)	Univariable *B* (SE)	Multivariable *B* (SE)	Univariable *B* (SE)	Multivariable *B* (SE)
Patient determinants										
Age	0.02 (0.02)	−0.01 (0.02)	0.001 (0.02)	−0.02 (0.02)	0.01 (0.01)	0.01 (0.02)	−0.002 (0.002)	0.001 (0.004)	0.002 (0.005)	0.005 (0.01)
MMSE	−0.08 (0.04)	0.04 (0.04)	−0.10 (0.05)	0.03 (0.03)	−0.04 (0.03)	0.002 (0.04)	0.001 (0.01)	−0.004 (0.01)	−0.0001 (0.01)	−0.01 (0.02)
CCI	0.08 (0.09)	0.01 (0.09)	0.002 (0.09)*	0.005 (0.08)	0.05 (0.07)	0.02 (0.09)	−0.01 (0.01)	0.01 (0.02)	0.01 (0.02)	0.02 (0.04)
NPI-Q severity	0.09 (0.02)[a]	0.02 (0.03)	0.18 (0.02)[a]	0.14 (0.02)[a]	0.05 (0.02)	0.03 (0.02)	−0.004 (0.004)	−0.004 (0.005)	−0.01 (0.01)	−0.01 (0.01)
Amsterdam IADL	−0.05 (0.01)[a]	−0.05 (0.01)[a]	−0.05 (0.01)[a]	−0.02 (0.01)*	−0.02 (0.01)	−0.01 (0.01)	0.001 (0.001)	−0.001 (0.002)	0.001 (0.003)	−0.002 (0.004)
Care partner determinants										
Age	0.02 (0.01)	0.01 (0.02)	0.01 (0.01)	0.01 (0.01)	0.01 (0.01)	−0.01 (0.02)	−0.004 (0.002)	−0.01 (0.003)	−0.003 (0.004)	−0.01 (0.01)
Sex, female	0.18 (0.23)	0.16 (0.19)	0.35 (0.25)	0.16 (0.16)	0.22 (0.17)	0.17 (0.19)	−0.06 (0.03)	−0.07 (0.04)	−0.09 (0.07)	−0.11 (0.07)
Relation to patient, spouse	0.70 (0.41)	0.28 (0.37)	0.49 (0.45)	0.04 (0.32)	0.46 (0.31)	0.44 (0.36)	−0.08 (0.06)	−0.05 (0.07)	−0.18 (0.12)	−0.14 (0.14)

*Significant based on $P < 0.05$.

[a]Significant based on $P < 0.01$.

Notes: Data are represented as beta coefficients (SE) and odds ratio (95% CI). Analyses were not corrected for multiple testing.

Abbreviations: CCI, Charlson Comorbidity Index; CI, confidence interval; EQ-5D, the European Quality of Life-5 Dimensions; GDS, Geriatric Depression Scale; IADL, Instrumental Activities of Daily Living; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; NPI-Q, Neuropsychiatric Inventory Questionnaire; RUD, Resource Utilization in Dementia; SCD, subjective cognitive decline; SE, standard error; VAS, Visual Analogue Scale.

TABLE 5 Univariable and multivariable linear regression models in AD dementia

	Informal care hours per day		NPI-Q caregiver distress		GDS		EQ-5D		VAS	
	Univariable *B* (SE)	Multivariable *B* (SE)	Univariable *B* (SE)	Multivariable *B* (SE)	Univariable *B* (SE)	Multivariable *B* (SE)	Univariable *B* (SE)	Multivariable *B* (SE)	Univariable *B* (SE)	Multivariable *B* (SE)
Patient determinants										
Age	−0.0001 (0.01)	−0.01 (0.02)	0.01 (0.01)	0.0002 (0.01)	−0.002 (0.01)	0.005 (0.01)	−0.001 (0.001)	−0.003 (0.001)	−0.01 (0.003)*	−0.01 (0.01)
MMSE	−0.02 (0.02)	0.01 (0.02)	−0.03 (0.02)*	0.01 (0.01)	−0.01 (0.01)	0.01 (0.01)	−0.001 (0.001)	−0.001 (0.001)	−0.003 (0.005)	−0.003 (0.05)
CCI	−0.10 (0.07)	−0.04 (0.09)	−0.02 (0.06)	0.03 (0.05)	−0.07 (0.04)	−0.04 (0.06)	−0.0004 (0.005)	0.01 (0.01)	−0.02 (0.02)	0.01 (0.03)
NPI-Q severity	0.04 (0.01)[a]	0.03 (0.01)*	0.13 (0.01)[a]	0.012 (0.01)[a]	0.04 (0.01)[a]	0.03 (0.01)[a]	−0.001 (0.001)	−0.001 (0.001)	−0.004 (0.003)	−0.003 (0.004)
Amsterdam IADL	−0.03 (0.01)[a]	−0.02 (0.01)[a]	−0.04 (0.01)[a]	−0.01 (0.004)[a]	−0.02 (0.004)[a]	−0.03 (0.005)*	0.0003 (0.0005)	−0.0001 (0.001)	0.002 (0.002)	0.002 (0.002)
Care partner determinants										
Age	0.02 (0.01)*	0.01 (0.01)	−0.004 (0.01)	−0.001 (0.01)	−0.003 (0.01)	−0.004 (0.01)	0.0001 (0.001)	0.0002 (0.001)	−0.001 (0.002)	0.0003 (0.004)
Sex, female	0.02 (0.15)	0.08 (0.16)	0.11 (0.15)	−0.004 (0.10)	0.27 (0.11)*	0.26 (0.11)*	−0.03 (0.01)*	−0.002 (0.01)	−0.07 (0.04)	−0.05 (0.05)
Relation to patient, spouse	0.84 (0.24)[a]	0.84 (0.29)[a]	−0.16 (0.23)	0.09 (0.17)	0.18 (0.17)	0.31 (0.21)	0.01 (0.02)	0.01 (0.02)	0.04 (0.06)	0.04 (0.09)

*Significant based on $P < 0.05$.

[a]Significant based on $P < 0.01$.

Notes: Data are represented as beta coefficients (SE) and odds ratio (95% CI). Analyses were not corrected for multiple testing.

Abbreviations: CCI, Charlson Comorbidity Index; CI, confidence interval; EQ-5D, the European Quality of Life-5 Dimensions; GDS, Geriatric Depression Scale; IADL, Instrumental Activities of Daily Living; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; NPI-Q, Neuropsychiatric Inventory Questionnaire; RUD, Resource Utilization in Dementia; SCD, subjective cognitive decline; SE, standard error; VAS, Visual Analogue Scale.

status also predisposed for more informal care time. In addition to behavioral symptoms of the patient, worse IADL functioning was also associated with increased NPI-Q caregiver distress. Finally, in addition to more behavioral symptoms and functional impairment in patients, also being a female care partner predicted more depressive symptoms. Female care partners reported lower QoL as measured using EQ-5D, but associations with VAS lost significance.

When we finally evaluated interactions with time interval to account for carrying the last observation forward, we generally found no interactions between time and dementia status, MMSE, or CCI. This indicates that the estimates in Table 3 do not vary as a function of the time between the measurements of dementia status, MMSE, and CCI and the variables measured through onlineADC. The only two significant interactions were between time and dementia status in the model with informal care time as the dependent variable (B[SE]) = 0.98 [0.49]) and between time and CCI in the model with EQ-5D as the dependent variable (B[SE] = 0.01 [0.004]). Both interaction terms indicate that the size of the associations between dementia status and informal care hours per day and between CCI and EQ-5D, respectively, increase as the time between the measurements increases, illustrating that our results may be an underestimation of the true effect size.

4 | DISCUSSION

The main finding of our study on outcomes in care partners of amyloid-positive patients with and without dementia was that being a female care partner, having a spousal relationship with the patient, and behavioral problems and functional impairment of the patients were associated with care partner burden in terms of informal care time, NPI-Q caregiver distress, depressive symptoms, and QoL. Behavioral problems and subtle functional impairment of the patient were associated with worse care partner outcomes in care partners of patients in the pre-dementia stages.

Previous studies on informal care time in AD dementia patients showed that care partners on average spend 6 to 8 hours on care per day.[5,41] We found a lower average informal care time in the AD dementia group of 4 hours per day. A possible explanation might be that the dementia patients in our sample had a relatively high MMSE and therefore a mild form of dementia. Similar to our study, previous studies in AD dementia showed that behavioral problems of the patient,[5,42] functional impairment of the patient,[5,41,43] and care partner living with the patient[5] were associated with more informal care time.

In line with previous studies, we demonstrated that a higher NPI severity leads to more NPI-Q caregiver distress.[44–46] Another study found that spouse care partners experienced more distress than care partners being differently related to the patient.[14] This result is also consistent with our results.

Furthermore, we showed that patient neuropsychiatric symptoms and functional impairment were associated with care partner depression, which is also in line with previous studies.[47,16]

Two previous review articles highlighted the need for more research on factors that contribute to care partner mental health disorders in AD.[18,19] These reviews showed that being female[18] and having a spousal[19] relationship with the patient were associated with more depressive symptoms. This differs from the findings presented in our study, as we found that behavioral symptoms and functional impairment were determinants of depressive symptoms, but being female and having a spousal relationship with the patient were not. These differences may be explained by the use of different scales to measure depression (i.e., Center for Epidemiologic Studies Depression Scale [CES-D],[48] Hospital Anxiety and Depression Scale [HADS],[49] and Profile of Mood States [POMS][50]) compared to our study in which we used GDS. These inconsistencies in results of the few available studies highlight the need for more research on depression in care partners, using the same depression scale.

Our results showed that female care partners had a lower QoL, measured with both the EQ-5D and a single VAS. This finding was also reported by previous studies on QoL of care partners in dementia.[15,51,52] Previous studies in AD focused on the association between the sex of the patient and care partner outcomes, but this study shows that care partner sex also has an impact on care partner outcomes.[53,54] Furthermore, patient characteristics were not significantly associated with care partner QoL in our study. This was also demonstrated by previous studies that showed that care partner QoL is mainly associated with physical and mental health of the care partner[15,17] and not with patient cognitive impairment.[51,55,56] Previous research has shown that EQ-5D may not be the optimal measure of the impact of caring for patients with AD on quality of life.[57] EQ-5D and VAS focus on health-related QoL and are more to measure the health of the care partner than the impact of the health of the patient on the QoL of the care partner. Nevertheless, EQ-5D and VAS are the most widely used questionnaires to measure QoL and therefore it is possible to compare our results to other studies. Because QoL of the care partner is an important outcome from the perspective of patients and their care partners,[58] more research is needed on how to assess QoL.

The global action plan from the World Health Organization (WHO) recommends supporting care partners to prevent a decline in their well-being.[59] Knowledge about the determinants of the care partner outcomes can be used to provide information and support to care partners at high risk of high burden. This study provides insight into which care partners may be a target for interventions, for example support groups and timely organization of formal care. We found that behavior and function were important determinants of care partner outcomes, even in the pre-dementia stages. This is also in line with a recent study, which showed that neuropsychiatric symptoms are prevalent across the full spectrum of AD.[60] Therefore, it is important to support care partners with non-pharmacological interventions for behavioral symptoms, such as case management, psychoeducation, and skill training.[61–63] Furthermore, our results suggest that maintaining the patient's independence may reduce caregiver burden, as functional impairment of the patient (measured by IADL) was associated with more care partner burden. In addition, we found that CCI was not associated with care partner outcomes. This indicates that AD severity of

the patient is associated with care partner burden and not the overall health of the patient.

Most previous studies on care partner outcomes focused on the dementia stage only, studying care partner burden by a single measurement (such as Zarit Burden Interview[64] or Caregiver Burden Inventory[65]), while not taking into account other relevant outcomes such as depressive symptoms and quality of life of the care partner. Finally, earlier studies lacked biomarker support of AD diagnosis, leaving open the possibility that results are not specific to AD. Our paper adds to the existing literature providing insight in determinants of a range of relevant outcomes (i.e., informal care time, NPI-Q caregiver distress, depression, and QoL) in care partner of biomarker-confirmed patients in the pre-dementia and dementia stages of AD.

This study also has some limitations. First, we included patients who were categorized as amyloid-positive based on amyloid-PET scan or abnormal CSF Aß$_{1\text{-}42}$. Current evidence suggests that CSF Aβ1-42/Aβ1-40 ratio provides a better estimate of AD pathology than CSF Aβ1-42, but unfortunately Aβ1-40 was not available in our sample.[66] Where possible, we used amyloid-PET to determine amyloid status. By using CSF biomarkers in addition to amyloid-PET, we were able to include a large group of care partners of amyloid-positive patients. A second limitation of this study is the length of time between dementia status diagnosis at the memory clinic and completing the onlineADC, for which we used last observation carried forward for dementia status, MMSE, and CCI. This could have resulted in misclassification and selective dropout. However, we classified patients based on the last available diagnosis to minimize potential misclassification. In addition, sensitivity analyses, taking into account time between diagnosis and completing onlineADC showed no interactions between time and dementia status, MMSE, or CCI. A third limitation is that selective drop-out may have led to an underestimation of care partner burden, because patients in a more advanced disease stage may have died before the questionnaires on care partner burden were administered or may not have been able to fill out the online questionnaires. Nonetheless, the online nature of the survey allowed us to include a large group of patients, including a large group of AD dementia patients, who otherwise may not have been able to travel to the clinic. A fourth limitation is that the size of the non-dementia group was rather small. The power may be too low to demonstrate small associations between determinants and care partner outcomes, particularly because associations are likely to be more subtle than in the dementia stage.

In conclusion, we showed that both patient (behavioral symptoms and functional impairment) and care partner determinants (female and spouse care partners) contribute to a range of detrimental care partner outcomes (i.e., informal care time, NPI-Q caregiver distress, depressive symptoms, and QoL) in amyloid-positive patients. Behavioral problems and subtle functional impairment of the patient were already associated with care partner outcomes in the pre-dementia stages. These findings provide red flags for identifying care partners in need of support and highlight targets most urgently in need of optimizing patient management.

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CONSENT STATEMENT

The study was approved by the local medical ethical committee. All patients provided written informed consent for their clinical data to be used for research purposes.Author disclosures are available in the supporting information.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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