



# Impact of Alzheimer's disease on the family caregiver's long-term quality of life: results from an ALSOVA follow-up study

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## Abstract

**Purpose** To examine caregivers' health-related quality of life (HRQoL) and well-being during the first 3 years after their family member's Alzheimer's disease (AD) diagnosis and assessed the relationship between caregivers' HRQoL, well-being, and the severity of AD. Further, to compare of caregivers' HRQoL to general population.

**Methods** Longitudinal design (36 months) after AD diagnosis of 236 caregiver–patient dyads. Linear regression was used to assess age- and gender-adjusted association between repeated measurements of caregivers' HRQoL and the severity

of AD. For comparison with general population, the National Health 2011 Health Examination Survey data was utilized.

**Results** Caregivers had significantly lower HRQoL than age- and gender-standardized counterparts. Severity of AD was significantly ( $p < 0.05$ ) associated with the mobility and depression dimensions of caregiver's HRQoL but not with the total HRQoL index score.

**Conclusions** Caregivers' HRQoL seems to deteriorate earlier than previously noted. The severity of AD has not that great impact on caregiver's HRQoL as assumed.

**Keywords** Family caregivers · Alzheimer's disease · Health-related quality of life · 15D · Psychological distress

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## Abbreviations

AD	Alzheimer's disease
ADCS-ADL	Alzheimer's Disease Cooperative Study Activities of Daily Living scale

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AIC	Akaike information criteria
CDR	Clinical Dementia Rating
CDR-SOB	Clinical Dementia Rating, Sum of Boxes
CT	Computed tomography
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
GEE	Generalized estimating equation
HRQoL	Health-related quality of life
MCI	Mild cognitive impairment
MMSE	Mini-mental state examination
MRI	Magnetic resonance imaging
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association
NPI	Neuropsychiatric inventory
QIC	Quasi-AIC
VAS	Visual analog scale

## Introduction

Family caregiving has become an established practice in caring for people with Alzheimer's disease (AD). Family caregivers' health-related quality of life (HRQoL) and well-being have been recognized as major elements in the success of home care [1–5] as well as predictors of institutionalization in persons with AD [1, 6].

HRQoL is a broad concept that is affected in complex ways by a person's physical health, psychological state, level of independence, social relationships, and relationship with salient features of his or her environment [7]. Cross-sectional studies have established an association between decreasing HRQoL and increasing caregiver burden [4, 8, 9], including decreased ability to maintain interests other than caregiving [10].

Family caregivers' HRQoL is affected by their subjective experiences, such as a feeling of burnout [3], depressive symptoms [11], sense of hope [12], and patient-related factors [8, 11]. The severity of the patient's neuropsychiatric symptoms has an impact on caregivers' HRQoL [8, 13]. An increase in the patient's dependence level [9] and more time-consuming daily caregiving [8, 9] were associated with lower HRQoL for caregivers. Further studies examining the association between patients' cognitive status and caregivers' HRQoL have yielded conflicting results. Markowitz et al. [8] found a significant relationship between caregivers' mental functioning aspects of HRQoL and caregivers' ratings of patients' cognitive, behavioral, and depressive symptoms. Despite recognition of the effect of these patient-related factors on family caregivers'

HRQoL, little evaluation of the relationship of caregiver HRQoL to AD severity has been previously conducted.

Therefore, we aimed to (1) characterize caregivers' HRQoL and well-being during the first 3 years of follow-up after their family member's AD diagnosis, (2) perform comparisons of caregivers with an age- and gender-standardized sample of the general population to assess the impact of caregiving on caregivers' HRQoL, and (3) assess the relationship between the HRQoL and well-being of the caregivers and the AD severity of the patients.

## Methods

### Study population

The present study analyzed data collected as part of the ALSOVA study. The design of the ALSOVA study has been reported previously [14, 15]. Briefly, AD patients and their family caregivers ( $n = 236$ ) were recruited from three memory polyclinics between 2002 and 2006, soon after a family member had received an AD diagnosis (on average within 5 months after the diagnosis). Caregivers had daily contact with their family member, and patients had a baseline of very mild (Clinical Dementia Rating, CDR 0.5) or mild (CDR 1) AD at diagnosis. All the family members with AD were home dwelling. Data on age, education, living arrangements, household composition were collected at the baseline and during the annual follow-up visits.

### AD diagnosis confirmation and assessment of progression

A family member presenting with neurodegenerative disorder was examined, and AD was diagnosed by a geriatrician or neurologist. The National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) [16] and the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) [17] criteria were used. A study neurologist confirmed the clinical AD diagnosis. All patients underwent diagnostic evaluation, including brain imaging (CT or MRI), and were advised to initiate AD-targeted drug therapy at the time of diagnosis or at the baseline visit.

The clinical parameters used in this study were measured at baseline and annually over the 3-year follow-up period by a trained study nurse or a psychologist. The severity of AD was evaluated using Clinical Dementia Rating Scale Sum of Boxes scores (CDR-SOB), range 0–18 [18]. Cognitive impairment was assessed using the mini-mental state examination (MMSE), range 0–30 [19], and activities of daily living were assessed using the Alzheimer's Disease Cooperative Study Activities of Daily Living scale (ADCS-ADL), range 0–78 [20, 21].

### Health-related quality of life

Caregivers' HRQoL and well-being were measured using the 15D instrument [22] and visual analog scale (VAS), respectively. The 15D is a generic, standardized preference-based utility measure that has both profile and single index score properties [22]. The 15D assesses 15 dimensions: mobility, vision, hearing, breathing, sleeping, eating, speech, excretion, usual activities, mental function, discomfort and symptoms, depression, distress, vitality, and sexual activity. These dimensions can be presented as profiles or as a single 15D index score, which is obtained by weighting all 15 dimensions with population-based preference weights that are assigned based on an application of the multi-attribute utility theory [23]. Both profile and index scores vary between 0 and 1, where 0 represents death and 1 represents perfect HRQoL. Recently, it has been shown that a difference of 0.015 in the 15D index score can be considered a minimal clinically important difference (in the sense that subjects can feel the difference) [24]. A directly elicited, vertical VAS scored from 0 (death) to 100 (full health) [25] was used as a measurement of well-being.

### Statistical analysis

Descriptive statistics were used to summarize data as percentages, means, standard deviation (SD), and 95 % confidence intervals (95 % CIs) as appropriate. To study the impact of caregiving on HRQoL, the AD caregivers were compared with a representative sample of the Finnish general population with corresponding 15D measurements obtained from the National Health 2011 Health Examination Survey ( $n = 7964$ ). [26]. Survey participants, who were in the age range of caregivers (i.e., 35–84 years of age), were selected from the population sample ( $n = 4458$ ). To enable statistical comparison, the population sample was weighted to reflect the age and gender distribution of the caregivers. Two-tailed  $t$  test was used to evaluate the significance of differences between the groups.

To study the age- and gender-adjusted relationship between the HRQoL (15D and VAS) and the severity of AD (CDR-SOB), we utilized repeated-measures linear regression using a generalized estimating equation (GEE) model. GEE models take into account the between-subject differences and within-subject correlations, such as those within longitudinal repeated-measures data. The GEE models were specified using a Gaussian distribution, identity link function, and unstructured correlation matrix. Goodness of fit of the GEE models was examined using Akaike information criteria (AIC) and residual plots (for goodness of fit of the mean models), as well as quasi-AIC (QIC) (for correlation structures in GEE models).

All analyses were conducted using IBM SPSS software for Windows, version 19.0, and STATA, version 9.2. The threshold used to define statistical significance was  $p < 0.05$ .

### Ethical considerations

The ethics committee of Kuopio University Hospital reviewed the ethical issues involved in this study (64/00) and approved the ALSOVA project. The study was approved by the Finnish Supervisory Authority for Welfare and Health and the Finnish Ministry of Social Affairs and Health.

The study was carried out in accordance with the Helsinki Declaration [27]. Willing participants were recruited on a voluntary basis. Both written and oral information about the study were given before participants were asked to give written consent. A consent form was signed by both the caregiver and the AD patient. The caregiver also provided proxy consent on behalf of the individual with AD. An initial visit was arranged soon after the diagnosis for those who gave consent. The voluntary nature of participation and the confidentiality of the data collected were emphasized at every study visit.

## Results

### Sample characteristics

Descriptive characteristics of the study sample are presented in Table 1. In brief, the mean age of caregivers was 65.7 years at the baseline and 67 % were female. The majority of caregivers (75 %) lived in the same household with the patient. The mean cohabitation time was 33 years (SD 1.7). A total of 108 (46 %) caregivers did not complete all three follow-up visits. Six (3 %) family caregivers and 27 (11 %) persons with AD died during the follow-up period. Analysis showed that the caregivers who completed the full three-year follow-up reported significantly milder depressive symptoms (BDI 8.42 vs. 10.5,  $p = .014$ ), better well-being at baseline (VAS 77.1 vs 72.4,  $p = .03$ ) but no significant difference on baseline 15D index. Also, better patient performance in activities of daily living was shown than the caregiver–patient dyads who were lost to follow-up (ADCS-ADL 66.3 vs. 62.4,  $p = .001$ ). In addition, patients' with full follow-up had numerically slightly better CDR-SOB (3.98 vs. 4.30,  $p = .10$ ).

### Caregivers' quality of life and well-being

The mean 15D index score of the caregivers stayed relatively stable with no statistically significant mean change

**Table 1** Demographic data for caregivers ( $n = 236$ ) and AD patients ( $n = 236$ )

Characteristics	Baseline ( $n = 236$ )	Year 1 ( $n = 198$ )	Year 2 ( $n = 168$ )	Year 3 ( $n = 131$ )
<i>Caregivers</i>				
Gender				
Male	33.5 % (79)	31.8 % (63)	33.3 % (56)	36.7 % (48)
Age				
	65.7 (11.9)	66.7 (11.8)	67.4 (11.9)	68.6 (11.8)
	(35–84)	(36–85)	(38–86)	(41–87)
5D index score	0.882 (0.087)	0.880 (0.085)	0.873 (0.092)	0.878 (0.093)
VAS score	75.0 (16.6)	74.8 (16.6)	72.6 (18.7)	71.4 (18.0)
<i>Patients</i>				
Gender				
Male	48.7 % (115)	47.0 % (93)	45.8 % (77)	43.5 % (57)
Age				
	75.6 (6.5)	76.5 (6.8)	77.5 (6.9)	78.5 (6.4)
ADCS-ADL	64.5 (8.9)	58.0 (12.7)	51.2 (15.9)	46.0 (18.4)
MMSE	21.5 (3.4)	19.3 (4.3)	17.5 (5.5)	16.4 (5.1)*
CDR-SOB	4.1 (1.5)	5.6 (2.3)	7.1 (3.0)	8.3 (3.4)**
CDR				
Very mild	54.2 % (128)	32.3 % (64)	16.1 % (27)	6.2 % (8)**
Mild	45.8 % (108)	56.6 % (112)	57.7 % (97)	58.1 % (75)**
Moderate	0 % (0)	11.1 % (22)	25.0 % (42)	31.0 % (40)**
Severe	0 % (0)	0 % (0)	1.2 % (2)	4.7 % (6)**

Values are presented as means (SD = standard deviation) or frequency (%;  $n/N$ )

15D Health-related quality of life (scale 0–1), VAS visual analog scale (scale 0–100), ADCS-ADL activities of daily living (scale 0–78), MMSE mini-mental state examination (scale 0–30), CDR-SOB Clinical Dementia Rating Sum of Boxes (scale 0–18), CDR Clinical Dementia Rating (scale 0–3)

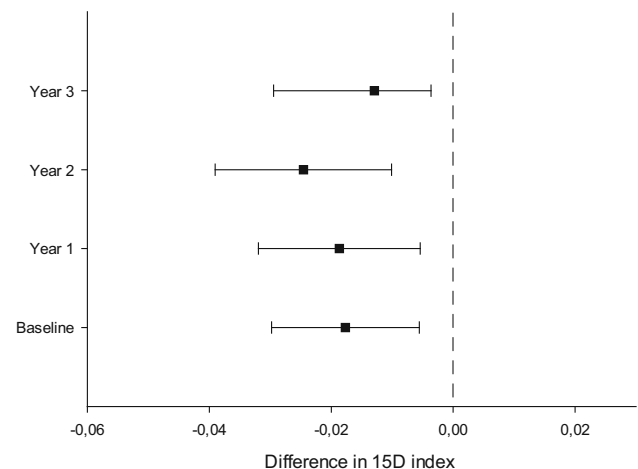
\* MMSE  $n=125$ ; \*\* CDR-SOB, CDR  $n= 129$

over the observed period. The average change from baseline was  $-0.008$  (95 % CI  $-0.019$ – $0.004$ ) over 3 years of follow-up. Caregivers' well-being (VAS) was at baseline 77.3 (95 % CI 74.8–79.9). It deteriorated significantly ( $p < 0.001$ ) to 73.9 (95 % CI 70.8–77.05) at the year three. The mean 15D score for the general population was 0.898 (SD 0.09) at the baseline and follow-up points 0.898 (SD 0.09), 0.987 (0.09), and, 0.892 (0.09), respectively.

### Caregivers' quality of life compared to that of the general population

The caregivers' mean 15D index score was already significantly poorer than the corresponding 15D index score of age- and gender-standardized general population at the time of the baseline measurement (mean difference  $-0.018$  (95 % CI  $-0.005$ – $0.029$ );  $p < 0.01$ ). This significant difference between caregivers and their age- and gender-standardized counterparts remained throughout the entire follow-up period (Fig. 1).

Family caregivers had significantly lower HRQoL than the general age- and gender-standardized population on



**Fig. 1** Mean difference with 95 % CI in the 15D index score between the caregivers and an age- and gender-standardized sample of the general population in different time points of measurement. A vertical dash line at zero indicates no difference between the groups, and negative numbers indicate poorer HRQoL for caregivers. A dashed line indicates no difference between groups

seven of fifteen HRQoL dimensions: vision, breathing, usual activities, depression, distress, vitality, and sexual activity (Fig. 2).

### Association between caregivers' QoL, well-being, and the severity of AD

Over the three-year follow-up period, the overall mean (95 % CI) annual increase in CDR-SOB was 1.65 (1.47–1.78) points per year ( $p < 0.001$ ). Although there was a significant association between the caregivers' age- and gender-adjusted well-being (VAS) and the AD severity, the association between caregivers' overall HRQoL (15D index) and patients' disease severity was not significant (Fig. 3). The age- and gender-adjusted VAS score decreased by 0.558 ( $p = 0.019$ ) for every one-unit increase in CDR-SOB scores. Within all 15 dimensions of HRQoL, only the mobility and depression dimensions were significantly associated with the severity of AD (CDR-SOB) (Fig. 4). The age- and gender-adjusted mobility and depression dimension score decreased by 0.004 ( $p < 0.01$ ) and 0.003 ( $p = 0.033$ ), respectively, for every one-unit increase in CDR-SOB scores.

### Discussion

This is the first comparison of family caregivers' 15D scores (HRQoL) to those of a sample of age- and gender-standardized general population in a longitudinal study setting we are aware of. The results indicate that family caregivers already have a significantly lower quality of life than their age- and gender-standardized counterparts by the time of AD diagnosis. Even though the overall HRQoL remained relatively constant during 36-month follow-up period, family caregivers scored lower on several dimensions of HRQoL. Patients' disease severity was correlated with caregivers' subjective well-being, but not with the overall HRQoL index score or the majority of the dimensional scores. The observed small change in the mean 15D score can be considered to be a minimally clinically important difference [24]; however, it was not statistically significant in the analyses presented here. The severity of AD may not have as great an impact on the caregivers' HRQoL as was previously concluded based on cross-sectional studies. [3, 8, 11]. However, the lack of significant effect over the course of the follow-up may be explained by the observation that caregivers' mean HRQoL had already significantly decreased by the time of AD diagnosis, thus reducing the magnitude of further changes after the diagnosis.

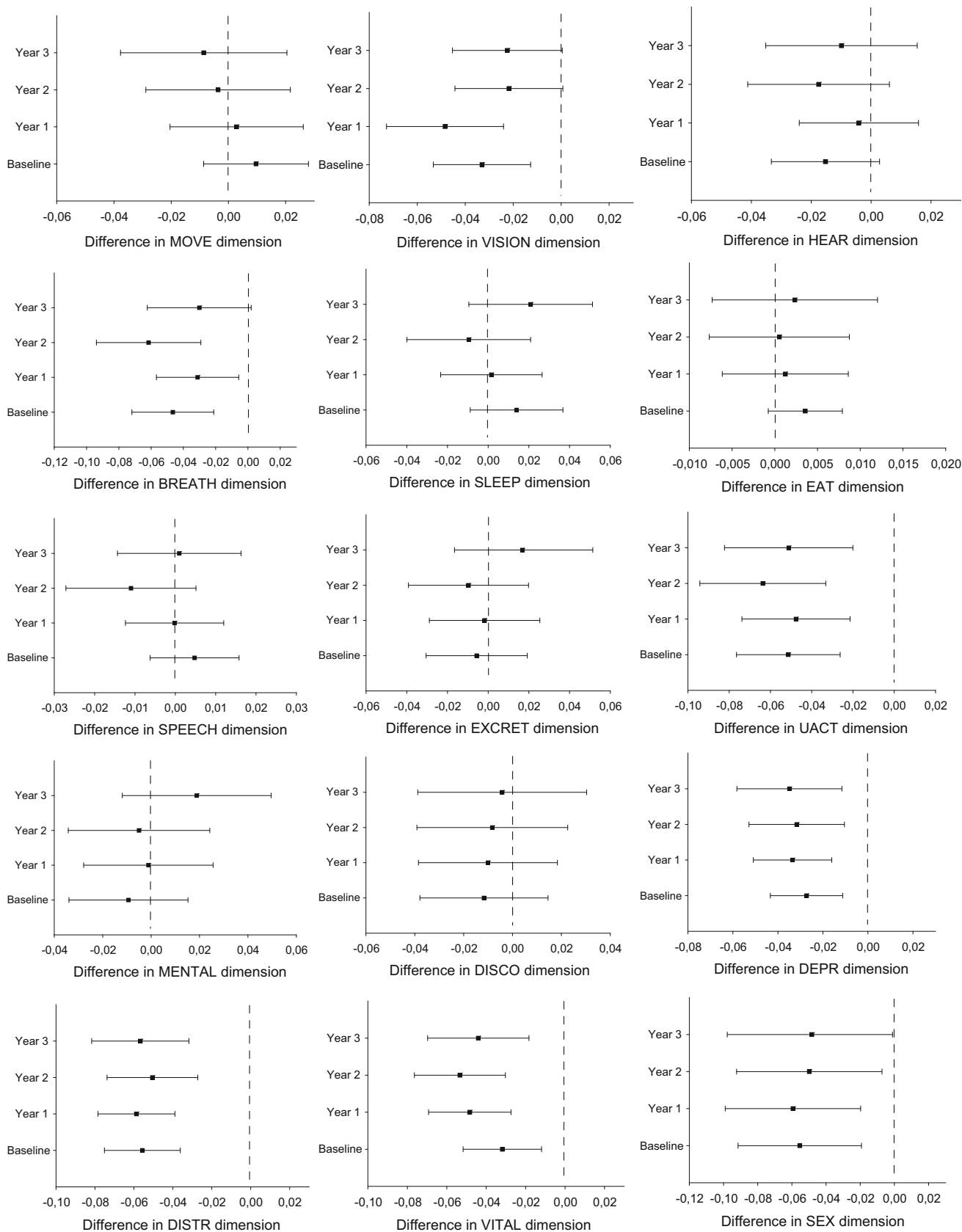
Our data suggest that caregivers' HRQoL deteriorates earlier than expected during the gradual decline in AD patients' cognition. Even though our patient sample was at a mild or very mild stage of AD at the baseline measurement, negative effects on caregiver HRQoL had already occurred. This could be explained by the observation that

the caregiving process begins very early, even before an early diagnosis of AD, [28] or the deterioration of HRQoL is rapid during the early days of caregiving. Further investigation of the caregiving process is warranted to determine when it starts and what characteristics define caregivers who will experience the greatest negative impact on their health and HRQoL. It should be noted that during the observed period a degree of accommodations might have occurred. However, we recognize possible selection bias during the follow-up. Contradictory findings exist in the literature regarding the impact on caregivers. In some reports, early caregiving was associated with increased burden [29, 30] and loss of intimacy [30] among caregivers for patients with mild cognitive impairment (MCI). However, in other studies, MCI caregivers were shown to experience normal levels of depressive symptoms, HRQoL, and sense of mastery [31, 32]. Thus, it is difficult to predict when or whether certain caregivers will start to suffer from psychosocial deficits causing weakening HRQoL, and this is an important issue for future research.

Although no previous longitudinal studies exist regarding dementia caregivers' HRQoL compared to an age- and gender-standardized population, our findings are supported by cross-sectional studies finding poorer HRQoL [33] and higher frequency of problems on each of the HRQoL dimensions compared with the general population [9] using different HRQoL scales.

In our study, family caregivers show differences from the general age- and gender-standardized population on seven of the HRQoL dimensions: vision, breathing, usual activities, depression, distress, and sexual activity. The physical components of HRQoL are strongly related to age and somatic conditions [34]. Furthermore, it is well documented that prolonged caregiving with dementia patients constitutes a risk to physical health and that caregivers are more likely to report their health to be fair or poor than non-caregivers [35]. Interestingly, no significant differences with respect to sleep were observed between caregivers and the general population during 36 months of follow-up. Sleep disturbances have previously been reported to relate to depressive symptoms and they may negatively affect QoL and health outcomes [5, 36]. Two-thirds of caregivers have reported sleep disturbances, but correlation with the severity of the patients' dementia or cognitive function was not observed [37].

Caregivers' relatively poor perceived HRQoL, particularly with respect to mental health and distress dimensions, has been shown previously using several instruments in different cultures [4, 38–40]. Our earlier cross-sectional results showed that a complex relationship exists between HRQoL and depressive symptoms, distress, and health-protective factors such as a sense of coherence [41]. The



**Fig. 2** Age- and gender-standardized measurements of individual health-related quality of life (15D) dimensions with 95 % CI. Family caregivers exhibited significantly lower HRQoL on seven of fifteen HRQoL dimensions (vision, breathing, usual activities, depression, distress, vitality, and sexual activity) when compared with the general age- and gender-standardized population. Vertical dash lines at zero indicate no difference between the groups. A dashed line indicates no difference between groups

impact of AD on intimacy and the sexual side of the relationship is evident in comparison with an age- and gender-standardized population. Our results corroborate previous findings that dementia reduces the importance of sexual relationship in couples [42, 43].

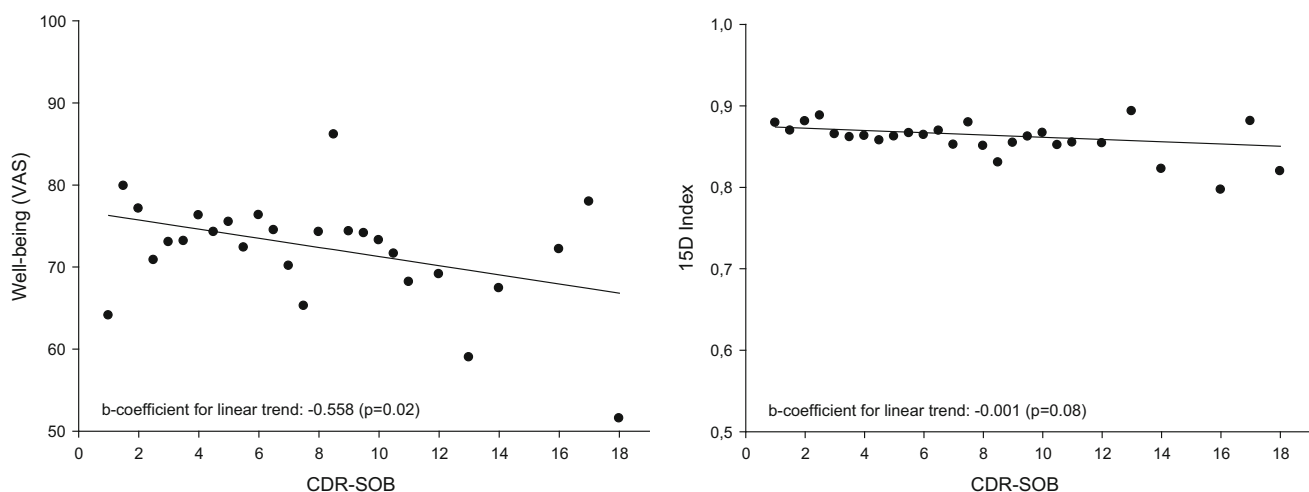
Our results demonstrate the impact of the disease severity (CDR-SOB) on the family caregivers' HRQoL on both mood- and burden-related dimensions, but not with respect to the overall HRQoL score. This finding agrees with that of a large cross-sectional study on HRQoL [44] where the AD stage did not significantly associate with the caregivers' HRQoL score. However, other studies report that low patient cognition, neuropsychiatric symptoms, and caregiver burden are associated with effects on caregivers' HRQoL [9–11], and some studies also report association with early institutionalization [1, 6].

A main strength of our study is the longitudinal design, starting at the time of early AD diagnosis, which is rare among HRQoL studies in caregiving settings. This study also features a comparison between our study population with an age- and gender-standardized control population. In the evaluation of AD severity, we used a global and

continuous measure CDR-SOB that does not appear to have the pitfalls of MMSE, in which previous reports suggest may inaccurately reflect the total impact, progression, and consequences of AD, and produce volatile estimates [45, 48]. When compared to the categorical version, CDR global rating, the continuous CDR-SOB provides a more detailed and sophisticated measure of disease severity, and is better suited for disease progression evaluation [46–48].

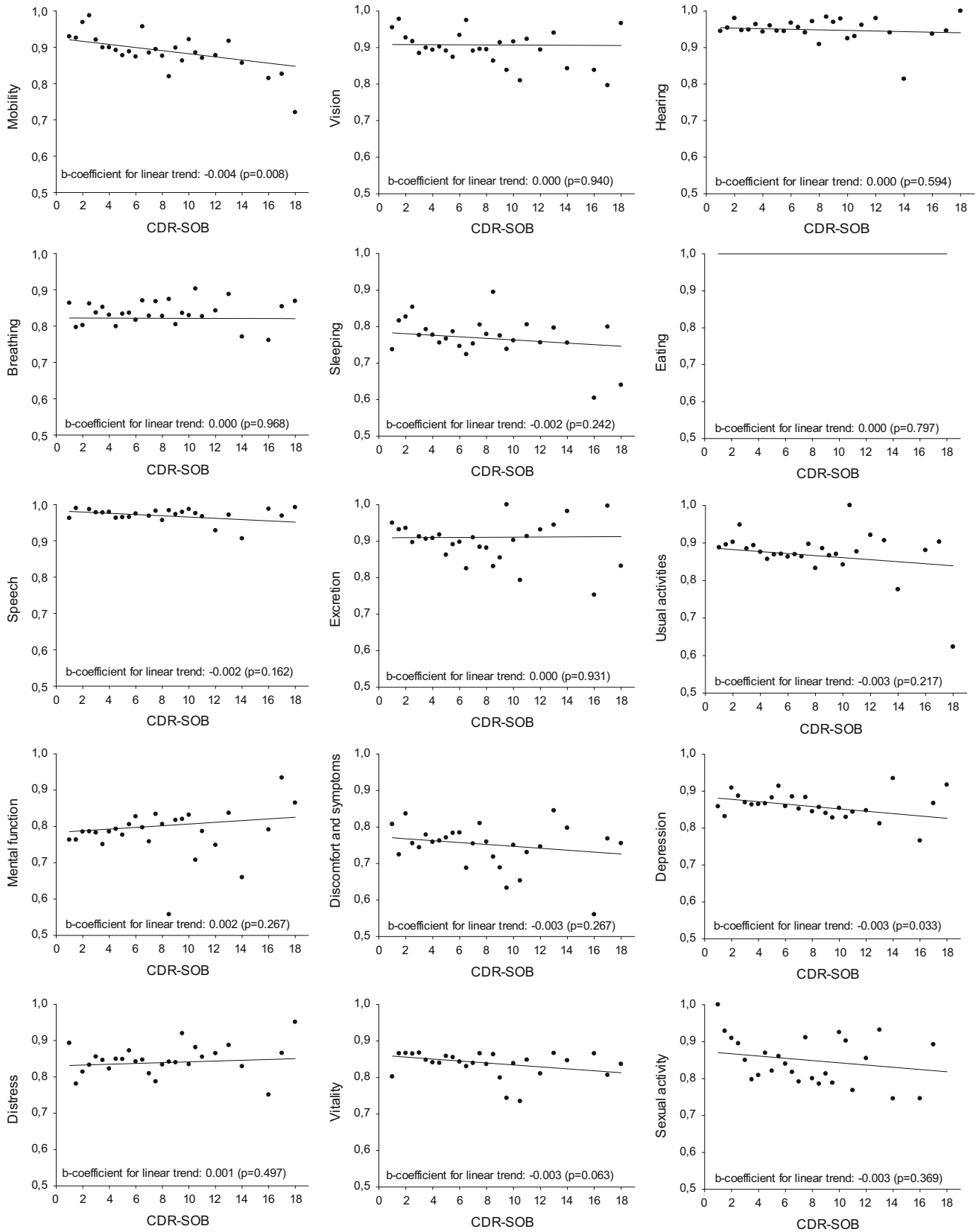
The fairly high dropout rate (46 %) is a potential limitation of this study; however, it is comparable with that seen in other caregiver studies having a similar design [48, 49]. Further limitation may be the possible selection bias of the primary recruiting process as the most burdened caregivers might refuse to participate to the follow-up study. As a subjective assessment, VAS includes all of the aspects that caregivers find to have impact on their well-being; however, there are limitations with the VAS, including possible bias in measurement due to multiple better and worse states presenting at the same time, or due to respondents' reluctance to choose values on either end of the scale [50]. In this sample, the significant better VAS score within those caregivers' with full follow-up data is a source of weakness in this study. Despite these limitations, the VAS proved to detect the deterioration of well-being within our sample.

The quality of AD patients' home care and their overall well-being rests greatly on their caregivers' ability to maintain a good quality of life. Caregivers HRQoL and subjective sense of well-being are fundamental to preserve. Along with postponing the patients' institutionalization,



**Fig. 3** Mean age- and gender-adjusted caregiver health-related quality of life (15D index) and well-being (VAS) scores in relation to patients' Alzheimer's disease severity trends, as determined by Clinical Dementia

Rating Sum of Boxes (CDR-SOB) measurement. Scores are adjusted using generalized estimating equations (GEE) with Gaussian distribution, identity link function, and unstructured correlation matrix





**Fig. 4** Mean age- and sex-adjusted caregiver health-related quality of life (15D) dimension scores, plotted in relation to patients' Alzheimer's disease severity, as determined by Clinical Dementia Rating Sum of Boxes (CDR-SOB) measurement. Scores are adjusted using generalized estimating equations (GEE) with Gaussian distribution, identity link function, and unstructured correlation matrix

taking care of the caregivers' own physical and psychosocial health has to be a priority of health care providers. Caregivers' depressive symptoms may turn out to be strong factors impacting HRQoL and well-being during the caregiving years.

Identification of the most vulnerable caregivers at the time of diagnosis can facilitate proactive, tailored support to promote the well-being of both patient and caregiver. Family caregivers live in close contact with their care recipients, and this should be considered in the development of these programs. Effective family-oriented support and need-based intervention programs to address caregivers' psychosocial resources and needs should be developed and provided along with more traditional care that focuses on the patient's condition.

Concluding, caregivers had significantly lower HRQoL than age- and gender-standardized counterparts and it remains considerable stable over caregiving period. The severity of AD (very mild, mild–moderate or severe AD) has not that great impact on caregiver's HRQoL as previously assumed.

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**Author contributions** Tarja Välimäki, Janne Martikainen, Anne Koivisto and Saku Väättäinen take the responsibility for the integrity of the data and the accuracy of the data analysis. Harri Sintonen carried out the comparisons with the general population. T.V., J.M., A.M.K. have full access to all data. All the authors have reviewed and approved the manuscript.

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#### Compliance with ethical standards

**Conflict of interest** Janne Martikainen is a senior partner of ESior Oy, which carries out health economic and outcome research studies for pharmaceutical companies, food industry companies, and hospitals. Saku Väättäinen is a paid employee of ESior Oy. Raquel Lahoz is a paid employee of Novartis Pharma AG. Harri Sintonen is the developer of the 15D.

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