CARERS' HEALTH-RELATED QUALITY OF LIFE IN ALZHEIMER'S DISEASE

REPORT BY THE DECISION SUPPORT UNIT

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ABOUT THE DECISION SUPPORT UNIT

The Decision Support Unit (DSU) is based at the University of Sheffield with members at York, Bristol, Exeter, Leicester, Warwick, Swansea and the London School of Hygiene and Tropical Medicine. The DSU is commissioned by The National Institute for Health and Care Excellence (NICE) to provide a research and training resource. Please see our website for further information www.nicedsu.org.uk.

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EXECUTIVE SUMMARY

The appraisals of lecanemab and donanemab for treating mild cognitive impairment (MCI) or mild dementia due to Alzheimer's disease (AD) included utility values for informal/unpaid carers. The appraisal committees and the External Assessment Groups (EAGs) preferred to use carers' EQ-5D values from the GERAS study, whereas the companies preferred to use carers' utilities derived from vignettes. The appeal panels concluded that the EQ-5D was inadequate to assess carer utility values in this population, and that the committee was unreasonable not to use other methods in this case. The National Institute for Health and Care Excellence (NICE) commissioned the Decision Support Unit (DSU) to independently review the carer utility sources considered in the appraisals and conduct a systematic literature review to determine whether the evidence suggests that EQ-5D is appropriate for measuring the health-related quality of life (HRQoL) of unpaid carers of people with AD.

Both appraisals modelled disease progression using state-transition models with states for MCI, mild AD, moderate AD, severe AD and death. Health states were further differentiated by whether patients were living at home in the community or institutionalised/living in a care home.

We reviewed the 13 studies reporting carers' EQ-5D scores that were discussed by the two companies in their submissions. We concluded that while none of these studies were ideally suited to inform all the model health states since they did not report the full range of severity by setting, they were aligned with NICE's preferences for measuring HRQoL and demonstrated that EQ-5D is widely used in measuring carers' HRQoL in AD.

We conducted a systematic literature review to identify studies that used EQ-5D to measure the HRQoL of carers of people with cognitive impairment or dementia due to AD. Our inclusion and exclusion criteria were designed to include relevant studies that analysed the effect of patient disease and aspects of caregiving on carers' HRQoL.

We found 36 additional studies and included 10 of the studies identified by the companies (3 were excluded according to our criteria), giving a total of 46 studies of the EQ-5D of carers in AD. Forty of these studies were cross-sectional, 26 of which analysed the relationship between carers' EQ-5D and one variable at a time (univariate analyses). We considered that univariate analyses were potentially subject to uncontrolled confounding since they did not account for other factors that may also affect the relationship between carer's EQ-5D and the individual variable. Instead, we focussed on the 20 studies that either reported either multivariate analyses (simultaneously analysing the effect of multiple variables on carers' EQ-5D) and/or

longitudinal studies that analysed the relationship between change in carer's EQ-5D and change in another variable. There were 15 multivariate analyses and 6 longitudinal analyses (one study reported both, hence a total of 20 studies).

We noted that the definition of carer varied between studies and was not always reported, and it was unclear whether additional carers were involved. The studies were from a mix of care settings: while many were conducted exclusively in the community, some also included patients in care homes, and some did not report the setting. Futthermore, studies rarely reported the level of formal care received at home, and no studies adjusted for this. These differences limit the comparability of studies and may limit their transferability to the populations under consideration in the economic models.

Considering together the evidence from the 20 studies, and grouping together variables that measured similar concepts, we identified five themes:

- *Caregiver burden*: Six of six studies found that increasing caregiver burden decreased carers' EQ-5D: the Zarit Burden Interview (ZBI) was the most common measure (in four studies). Four studies found statistically significant associations between ZBI and carers' EQ-5D, although some found non-significant relationships at one time point, and others described the correlation as weak. An increase in one point on the ZBI 22-item 0-88 scale decreased carers' EQ-5D by approximately 0.01, and an increase in one point on the ZBI short-form 12 item 0-48 scale decreased carers' EQ-5D in the range of 0.002 to 0.006.
- *Patient HRQoL*: Two of two studies found a statistically significant relationship between carers' EQ-5D and carers' proxy-reported patient HRQoL. One study found a significant relationship only between carers' EQ-5D and the patient's pain score which was proxy-reported by the carer. Two of two studies did not find a statistically significant relationship between carer's EQ-5D and patient-reported patient HRQoL
- *Disease severity*: Three of five studies found statistically significant relationships between patient AD severity and carers' EQ-5D (greater severity was associated with lower carers' EQ-5D scores) but these same studies also found some increases in patient severity were not statistically significantly associated with worsening carers' EQ-5D. Two studies found no statistically significant relationships.
- *Care setting*: Three of five studies found whether the patient lived at home or in a nursing home was not statistically significantly associated with carers' EQ-5D. One study found admission to a care home was associated with short, but not long-term

changes in carers' EQ-5D. Another found carers of patients living in nursing homes had statistically significantly higher EQ-5D scores than carers of patients who lived at home.

- *Duration of care*: Two of two studies did not find a statistically significant relationship between duration of caring and carers' EQ-5D.

We considered the key finding is that carers' EQ-5D is sensitive to changes in a validated measure of caregiving burden: the ZBI. This suggested that EQ-5D is appropriate for detecting changes in carers' EQ-5D due to caregiving demands. The direction of effect was as expected (a higher burden leads to lower EQ-5D scores) and the effect size was fairly consistent across studies. Extrapolating this relationship across the full range of ZBI scores suggested disutilities in the range of 0 to -0.1 for no-mild burden, -0.02 to -0.20 for mild to moderate burden, -0.04 to -0.30 for a moderate to severe burden, and -0.04 to -0.44 for a severe burden. Translating these into the health states in the model and primarily using the upper bound estimates from the ZBI-12 relationship (since this has more accuracy and is based on a UK study) with the midpoint coefficient of -0.004, supplemented with the coefficient of -0.006 for the most severe state suggests plausible disutility estimates could be -0.04 for MCI, -0.08 for mild AD, -0.192 for moderate AD and -0.288 for severe AD. We recognised that the upper bounds of these disutilities were somewhat larger than those derived from the GERAS study and considered that this was because the ZBI scores in the GERAS study (and other similar studies) were compressed into a much smaller range. It was unclear how the mini mental state examination (MMSE) categories in GERAS corresponded to the model health states, and how these corresponded to ZBI scores.

The carer disutilities derived from the vignettes were much larger than those reported for carers' EQ-5D linked to patient AD severity in the literature. While we considered that the vignettes were generally well conducted, we were concerned that the omission of some generic domains of HRQoL from the vignettes meant that they are subject to focussing effects, which may have led to artificially low scores and increased differences between health states. More fundamentally, we do not believe that evidence has been systematically identified to demonstrate that EQ-5D is not valid in this population.

We believe that our systematic review has confirmed that EQ-5D is appropriate in this population and has provided estimates of the range of EQ-5D disutilities that may correspond to levels of caregiving burden. However, there remains an evidence gap for UK-specific carer's EQ-5D data in this population that adjust for confounders including formal care and other

unpaid carers and can be directly used to populate economic models structured around patient AD severity and setting.

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ABBREVIATIONS AND DEFINITIONS

AARS	Agitation/aggression and related symptoms
AD	Alzheimer's disease
ANCOVA	Analysis of Covariance
ASCOT-Carer	Adult social care outcomes toolkit for carers
CarerQoL	Carer quality of life
BDS	Berger Dementia Scale
BPSD	Behavioral and psychological symptoms of dementia
CANE	Camberwell Assessment of Need for the Elderly
CDQLP	Community Dementia Quality-of-Life Profile
CDR	Clinical Dementia Rating
CDR-SB	Clinical Dementia Rating Sum of Boxes
CES	Carer Experience Scale
CI	Cognitive impairment
DEMQOL	Dementia quality of life
DSU	Decision Support Unit
EAG	External Assessment Group
EQHAW	EQ Health and Wellbeing
EQ-5D-3L	EQ-5D 3-level version
EQ-5D-5L	EQ-5D 5-level version
EQ-5D VAS	Visual Analogue Scale
FAST	Functional assessment staging in AD
GDRS	Global Deterioration Scale
GHQ-12	General Health Questionnaire-12
HC	Home care
HINT-8	Health-Related Quality of Life Instrument with 8 items
HRQoL	Health-related quality of life
HUI3	Health Utilities Index 3
ICECAP-A	ICEpop CAPability measure for Adults
ICECAP-O	ICEpop CAPability measure for Older people
ICD	International Classification of Diseases
ICER	Incremental Cost-Effectiveness Ratio
ILTC	Institutional long-term care
IQR	Interquartile range
LTCI	Long-term care institution

MCI	Mild cognitive impairment
MMSE	Mini-Mental State Examination
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NPI	Neuropsychiatric Inventory
NR	Not reported
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
PwD	People with dementia
QALY	Quality-adjusted life year
SD	Standard deviation
SF-6D	Short Form 6 dimensions
STA	Single health technology appraisal
T-IADL	Time spent on instrumental activities of daily living
TSD	Technical Support Document
TTO	Time trade-off
VAS	Visual Analogue Scale
ZBI	Zarit Burden Interview

1. INTRODUCTION

The National Institute for Health and Care Excellence's (NICE's) health technology evaluations manual specifies that the reference case perspective on outcomes includes *"all health effects, whether for patients or, when relevant, carers"* in Section 4.3.17 and Table 4.1, or *"all relevant health effects, whether for patients, or when relevant, other people (mainly carers)"* in Section 4.2.8.[1] The manual specifies that health effects should be expressed in quality-adjusted life years (QALYs) (Section 4.2.14), which reflect length of life and health-related quality of life (HRQoL) (Section 4.3.2).

The NICE manual states that the EQ-5D is the preferred measurement method for HRQoL in adults (Section 4.3.6). Where EQ-5D is not available from clinical trials, it can be sourced from the literature (Section 4.3.8), or from mapping other HRQoL measures onto EQ-5D (Section 4.3.9). The manual acknowledges that there are some circumstances in which EQ-5D is not the most appropriate measure and describes the evidence that should be presented to make this case (Section 4.3.10): qualitative empirical evidence on lack of content validity, and evidence of poor construct validity and responsiveness from a synthesis of peer-reviewed literature. In this scenario, alternative HRQoL measures may be used, accompanied by a detailed account of the methods and their validity – the order of preference is (Figure 4.1):

1. Other generic preference-based measure
2. Condition-specific preference-based measure
3. Vignettes
4. Valuation of own health

In April 2026, the NICE asked the Decision Support Unit (DSU) to provide additional advice on the evidence used to inform caregiver utilities in two ongoing single health technology appraisals (STAs) of lecanemab and donanemab for the treatment of mild cognitive impairment or mild dementia caused by Alzheimer's disease (AD).[2] The appeal panels for both STAs upheld the appeal points that the committee's conclusion on utility values for caregivers does not reflect the available evidence.[3, 4] In both appraisals, the committee preferred to use the EQ-5D values reported by Reed *et al.*[5] based on the observational GERAS study. The EQ-5D utility values from GERAS study showed a small difference of 0.04 between mild to severe AD, whereas the utility values derived from one of the company's vignette studies showed a larger difference. The appeal panel highlighted concerns regarding the appropriateness of EQ-5D measure to assess caregiver utility values in AD and noted that the committee had the discretion to use other methods when EQ-5D is inadequate.[3, 4]

This report is set out as follows. Section 2 provides the aims and objectives of this project. Section 3 describes the summary and the critique of the caregiver utility evidence identified by the companies and the EAGs in both appraisals. Section 4 summarises the methods and findings of the systematic review of studies on EQ-5D in caregivers of people with cognitive impairment or dementia due to AD. Section 5 presents the conclusions and recommendations. Section 6 discusses the work and its limitations.

2. AIMS AND OBJECTIVES

This project aimed to understand whether evidence shows that EQ-5D is appropriate for measuring HRQoL of carers of people with AD, in the context of the lecanemab and donanemab appraisals. It further aimed to identify any additional sources of caregiver utilities that may be useful for populating the economic models in these appraisals.

The project was conducted in two stages. Stage 1 was a review of the carer utility evidence identified by the companies and EAGs in the appraisals of lecanemab and donanemab, to consolidate evidence from the two appraisals into one place, and to understand the existing evidence base for the use of EQ-5D or other measures in carers' HRQoL in AD. Stage 2 was a systematic literature review to identify further studies reporting EQ-5D in carers of people with AD, and assessment of whether EQ-5D is appropriate in this population.

3. STAGE 1

Both appraisals use state-transition models with five mutually exclusive health states:

- Mild cognitive impairment (MCI) caused by Alzheimer's disease (Clinical Dementia Rating Sum of Boxes [CDR-SB] score of 0.5)
- Mild dementia caused by Alzheimer's disease (CDR-SB score of 0.5 or 1)
- Moderate dementia caused by Alzheimer's disease (CDR-SB score of 2)
- Severe dementia caused by Alzheimer's disease (CDR-SB score of 3)
- Death

Within each (alive) health state, people can be in the community setting or residential care. People can transition from the community setting to residential care, but not from residential care into the community setting.

3.1. Caregiver HRQoL values identified in the lecanemab appraisal

Clarity AD included caregiver EQ-5D 5-levels (EQ-5D-5L). In their original submission, the company used this, mapped to 3L using the Hernandez algorithm, for the MCI due to AD and mild AD health state. The company stated that there were insufficient observations to inform

moderate or severe, and no data for carers of institutionalised patients, and so they conducted literature searches to identify values for these health states.

In their initial submission, the company for lecanemab described that they undertook a systematic literature review to identify health state utilities for patients and carers. They stated that they identified eight potential sources of caregiver HRQoL for the UK: Woods *et al*. 2012,[6] Bradshaw *et al*. 2013,[7] Bleijlevens *et al*. 2015,[8] Black *et al*. 2018,[9] Handels *et al*. 2018,[10] Dixit *et al*. 2020,[11] Farina *et al*. 2020[12] and Fang *et al*. 2016.[13] Of these, the company stated that only three reported caregiver HRQoL by disease severity: Black *et al*. 2018, Farina *et al*. 2020 and Fang *et al*. 2016. The company highlighted an additional three non-UK studies that reported caregiver HRQoL by health state: Van Hezik-Wester *et al*. 2023,[14] Lopez Bastida *et al*. 2006,[15] and Mesterton *et al*. 2010.[16] These studies are discussed in Section 3.3

The company later revisited its approach for modelling in response to draft guidance, citing a study by Reed *et al*. 2017[5] suggesting that EQ-5D may be a suboptimal measure in this population, and preferring to use utilities from vignettes presented within the donanemab appraisal. The vignette studies are discussed further in Section 3.4.

3.2. Caregiver HRQoL values identified in the donanemab appraisal

The clinical trials for donanemab did not collect caregivers' HRQoL. In their initial submission, the company for donanemab described that they undertook a systematic literature review and identified 30 studies for patients and their caregivers. The company stated that three of these were conducted in the UK and collected EQ-5D for caregivers: Fang *et al*. 2020,[13] Froehlich *et al*. 2021[17] and the GERAS study described by Reed *et al*. 2017.[5] These studies are discussed in Section 3.3

The company conducted two vignette studies to generate HRQoL values for carers of people with Alzheimer's disease:

1. For carers of people with MCI or mild dementia in the community and residential settings, and for people with moderate dementia in the community setting[18, 19]
2. For carers of people with moderate dementia in the residential setting and people with severe dementia in community and residential settings[20]

The two vignette studies used time trade-off approaches and general population participants. Both considered separate descriptions for caregivers who were children or spouses of the patient. The vignette studies are discussed further in Section 3.4.

3.3. Caregiver HRQoL values from the literature

The 13 studies identified across the two appraisals are summarised in Table 1. Generally, the studies found that caregivers' EQ-5D ranged from approximately 0.7 to 0.9, with carers of patients in more severe states reporting lower HRQoL in unadjusted comparisons, but few studies reporting statistically significant differences when adjusting for other variables.

Ideally, to inform the economic model health states, studies would report caregivers' EQ-5D by both patient severity and setting (community or care home). However, these two factors are likely to be correlated (patients with more severe disease are more likely to transition into institutional care), but many studies either did not report the setting or described different proportions of patients in institutional care across severity states and did not formally adjust for this. Some studies excluded caregivers where the patients transitioned into institutional care, for example in Reed *et al*. (2017),[5] 214 of 1495 initially recruited caregivers discontinued before 17 month visit because the patient had been institutionalised. Only Farina *et al*. (2020)[12] report a regression analysis for carers' EQ-5D adjusting for both patient severity (measured by mini mental state examination (MMSE)) and residential setting (binary variable for care home), and they found that neither were statistically significantly. However, it is possible that there is some level of multicollinearity between these two variables, making it difficult to isolate their individual effects. In this regression analyses, only patients' HRQoL as measured by Dementia quality of life (DEMQOL)-Proxy and Zarit Burden Interview (ZBI) were statistically significantly associated with carers' EQ-5D.

Furthermore, ideal studies would be longitudinal in design and follow caregivers' HRQoL trajectories as the patient's disease progressed. This would allow researchers to isolate the effect of worsening disease severity (and institutionalisation), since change in carers' HRQoL could be analysed. Cross-sectional studies are prone to selection bias (people who become or remain carers of patients at different severities differ from people who do not, and the same factors that affect the probability of someone being a carer also affect their HRQoL). Eight of the studies were cross-sectional, and five were longitudinal but the follow up time was typically less than two years, and analyses are not presented for change in carers' HRQoL where patients transitioned between health states. For either study design, it is important to adjust for potential confounders such as the carers' age and sex when comparing HRQoL between different populations.

3.3.1. Caregivers' HRQoL by patient severity

Eight studies reported caregivers' HRQoL by patient severity.

Black *et al*. (2018)[9] reported that unadjusted (raw) caregiver EQ-5D scores were statistically significantly lower for more severe patient health states (ranging from prodromal to severe). In their regression analysis adjusting for other potential confounders, EQ-5D scores were statistically significantly worse for moderate versus mild (-0.03), but not for severe versus moderate (-0.02) or mild versus prodromal (-0.018). ZBI was significantly worse for moderate versus severe and severe versus mild. This study did not report setting so it is unknown whether patients were receiving care at home or lived in an institution, or how this distribution varies across health states. There is a potentially an unknown level of confounding due to this omitted variable.

Farina *et al*. (2020)[12] reported that unadjusted caregiver's EQ-5D scores were not statistically significant lower for more severe states (mild:0.8, moderate: 0.8, severe:0.9). However, the proportion of patients living in care homes varied between health states and increased with severity, potentially confounding the results.

Fang *et al*. (2016)[13] reported median EQ-5D scores for carers of patients in mild and moderate states as 0.81 and 0.80 but did not formally compare these or present any adjusted analysis. The distribution of patients between home care and institutions is not reported.

Mesterton *et al*. (2010)[16] reported that caregiver unadjusted EQ-5D scores did not vary significantly by patient disease stages, but the bar chart presented shows a trend with mean scores lower for more severe states. They reported the proportion of patients living at home, which is lower for more severe states and is not adjusted for in the analysis, potentially confounding the results.

Van Hezik-Wester *et al*. (2023)[14] reported that unadjusted carer EQ-5D scores for patient health states are numerically but not statistically significantly lower for more severe states (mild: 0.858, moderate: 0.865, severe: 0.866). They reported the proportion of patients institutionalised, which is higher for more severe states and is not adjusted for in the analysis, potentially confounding the results.

Reed *et al*. (2017)[5] reported that baseline unadjusted carers' EQ-5D scores are lower (p=0.043) for more severe states (mild: 0.86, moderate: 0.85, severe: 0.82). No patients were institutionalised at baseline, and institutionalisation was the most common reason for discontinuation (n=214).

Froehlich *et al*. (2021)[17] reported that carers' EQ-5D scores were not statistically significantly different at baseline (mild: 0.85, moderate: 0.85). No patients were institutionalised at baseline.

Lopez-Bastida *et al*. (2006)[15] reported that carers' EQ-5D scores did not vary statistically significantly by patient disease severity, with a mean of 0.67. It is unclear whether any patients were institutionalised and whether this confounds the results.

3.3.2. Caregivers' HRQoL by setting

Bleijlevens *et al*. (2015)[8] and Bradshaw *et al*. (2013)[7] are both longitudinal studies that report the change in carers' EQ-5D when the patient was admitted to residential care. However, both were studies of caregivers only (not patient-caregiver dyads) and do not report information on the patient's severity. The level of confounding between patient severity and institution is therefore unknown.

Bleijlevens *et al*. (2015) analysed the change in EQ-5D for carers of 126 people with Alzheimer's disease who were deemed at risk of admission to an institutional long-term care (ILTC) facility (as judged by a professional caregiver) at baseline and transitioned from home to an ILTC facility within 3 months. They found that while carers' ZBI and General Health Questionnaire-12 (GHQ-12) statistically significantly improved (from 35.4 to 22.4 and from 14.2 to 12.0 respectively), carers' EQ-5D did not change (remained at 0.77). Bleijlevens *et al.* (2015) also compared the EQ-5D of 791 caregivers of people with Alzheimer's disease living in ILTC compared with 1223 caregivers of people with Alzheimer's disease living at home in a cross-sectional analysis and found that home caregivers had statistically significantly worse EQ-5D (0.75 versus 0.77, p=0.035). The authors noted that taking care of people with Alzheimer's disease at home is likely to impose higher demands on informal caregivers, but that there is likely to be a relationship between the course of burden and course of transition, with a particularly high burden for home caregivers in the period immediately preceding transition to ILTC.

Bradshaw *et al*. (2013) found no statistically significant change in EQ-5D, carer strain or GHQ-12 for 38 carers of people with cognitive impairment who moved from community to a care home at 6 months. In their cross-sectional baseline analysis, Bradshaw *et al*. (2013) found lower EQ-5D scores for caregivers of patients living in the community (median 0.73 for 58 carers living with the patient) than for 51 carers of patients living in care homes (median 0.85) but that these differences were not statistically significant.

Van Hezik-Wester *et al*. (2023)[14] found that 36 caregivers of people with Alzheimer's disease who were living in the community had higher EQ-5D-5L scores than 32 caregivers of people who were institutionalised (0.832 vs 0.758), but that these differences were not statistically significant. This study collected data on patient severity and the proportion of patients who were institutionalised increased as severity worsened.

Table 1: Summary of studies in appraisals

Author (year)	Country	Definition of caregiver	Sample size	Study design	Health states	Setting	HRQoL measure	Unadjusted outcomes	Adjusted outcomes	Funder
Black (2018)[9]	France, Germany, Italy, Spain, the UK, and the US	Person accompanying the patient to their consultation	1,201	Cross-sectional	Defined by MMSE. pro-domal (27-30), mild (21-26), moderate (10-20), severe (< 10)	Not reported	EQ-5D-3L	severe: 0.807, moderate: 0.862, mild: 0.886, prodromal: 0.896 *	Mild vs prodromal: -0.018. Moderate vs mild: -0.033*. Severe vs moderate: -0.02.	Merck
Farina (2020)[12]	UK	self-identify themselves as a carer for the person with dementia,	377	Cross-sectional	Defined by MMSE Mild (>=20), moderate (10-19), severe (0-9)	Mixed: some patients in care homes	EQ-5D-3L	Mild: 0.8, moderate: 0.8, severe: 0.9	Dementia severity, and residential care home setting were not significantly	

Author (year)	Country	Definition of caregiver	Sample size	Study design	Health states	Setting	HRQoL measure	Unadjusted outcomes	Adjusted outcomes	Funder
									associated with carers EQ5D after controlling for other confounders.	
Fang (2016)[13]	Canada	Primary informal caregiver	216	Cross-sectional	Mild and moderate (not defined)	Not reported	EQ-5D-3L (UK value set)	Medians. Mild: 0.81, moderate: 0.80.	Not reported	Canadian Institutes of Health Research
Handels (2018)[10]	8 European countries including UK	Informal caregiver	451 UK = 76	Cross-sectional	Defined by MMSE. Mild or moderate (<=24)	Home-dwelling	EQ-5D-5L	UK: 0.81		EU Joint Programme – Neurodegenerative Disease Research
Mesterton (2010)[16]	Sweden	Identifiable and reliable primary caregiver for patients not in	233	Cross-sectional	Defined by MMSE. Mild: 20-26. Moderate:	Community and residential care – higher	EQ-5D-3L	Carer EQ-5D lower for more severe but not	NR	Pfizer AB

Author (year)	Country	Definition of caregiver	Sample size	Study design	Health states	Setting	HRQoL measure	Unadjusted outcomes	Adjusted outcomes	Funder
		residential care. For patients in residential care, member of staff could respond if no informal caregiver identified			10-19. Severe: 0-9.	proportion of severe patients in residential care		significantly. All in range 0.7-0.8 (presented as bar chart)		
Dixit (2021)[11]	England	Caregiver, not defined	26	Cross-sectional	NA	Community dwelling	EQ-5D-3L	Mean: 0.7		NIHR, University Hospital Southampton NHS trust
Bleijevens (2015)[8]	8 European countries including England	Informal carers of PwD recently admitted to ILTC (visited twice a week) Informal carers of PwD receiving formal care at	2014 total, 157 in England	Longitudinal	NA	Recently admitted to long term care, or receiving formal care at home and at	EQ-5D-3L UK	Caregiver EQ-5D England ILTC: 0.80, HC: 0.79	No change in caregiver EQ-5D follow admission to ILTC (0.77 vs 0.77)	European Commission

Author (year)	Country	Definition of caregiver	Sample size	Study design	Health states	Setting	HRQoL measure	Unadjusted outcomes	Adjusted outcomes	Funder
		home, at risk of admission.				risk of admission				
Woods (2012)[6]	England and Wales	Relative or other caregiver who maintained regular contact	486	Interventional, longitudinal	Intervention (reminiscence) or control at baseline, 3 months, 10 months	Community	EQ-5D	Intervention: baseline 0.75, 3 month 0.78, 10 month 0.79. Control: baseline 0,76, 3 month 0.77, 10 months 0.77	Treatment effect at 3 months: 0.10 (not statistically significant)	
Bradshaw (2012)[7]	UK	Someone who has regular contact with the patient participant for at	201	Longitudinal	Carers lives with patient, elsewhere, or patient lives in care home	Mix community and care homes	EQ-5D-3L	Median. Carer lives with patient: 0.73, Carer lives elsewhere:	No change in carer EQ-5D at 6 months, including where	NIHR

Author (year)	Country	Definition of caregiver	Sample size	Study design	Health states	Setting	HRQoL measure	Unadjusted outcomes	Adjusted outcomes	Funder
		least an hour a week						0.81, patient lives in care home: 0.85	community resident moved to care home.	
Van Hezik Westers[14]	Netherlands	in the last 2 weeks, they have been providing unpaid care to someone with a physician confirmed AD diagnosis	68	Cross-sectional	AD health states, described by symptoms: MCI, mild AD, moderate AD, and severe AD	Mixed community and institutionalised	EQ-5D-5L	Mild: 0.821, moderate: 0.762, severe: 0.834	NR	Biogen
Lopez Bastida[15]	Spain	Primary caregivers	237	Cross-sectional	Clinical Dementia Rating Scale (CDR) Mild (1), moderate	Outpatient care	EQ-5D-3L	Mean: 0.67. None of the differences among the caregivers' EQ-5D summary	NR	Fundacion de Estudios de Economia Aplicada

Author (year)	Country	Definition of caregiver	Sample size	Study design	Health states	Setting	HRQoL measure	Unadjusted outcomes	Adjusted outcomes	Funder
					(2), severe (3)			scores by disease stage were significant		
Reed (2017)[5]	France, Germany, UK	Primary caregiver, responsible for the patient for at least 6 months per year	1,495	Longitudinal	Defined by MMSE. mild (21-26), moderate (15-20), moderately severe / severe (<=14)	Community dwelling	EQ-5D-3L	mild: 0.86, moderate: 0.85, mod severe/severe: 0.82, *	the change from baseline to 18 months in the overall sample was not significant and did not differ significantly across the AD dementia severity	Eli Lilly

Author (year)	Country	Definition of caregiver	Sample size	Study design	Health states	Setting	HRQoL measure	Unadjusted outcomes	Adjusted outcomes	Funder
									groups (data not shown)	
Froehlich (2021)[17]	Germany, UK, Spaim	primary caregivers (defined as spending at least 7 hours a week caring for the patient)	616	Longitudinal	MMSE. Mild: 21-26. Moderate: 10-20.	Community dwelling	EQ-5D-5L	Baseline. Mild: 0.88. Moderate: 0.88	Change over 18 months. mild: -0.03, moderate: -0.07 (not significant)	Merck

AD - Alzheimer's Disease, EQ-5D-3L - EQ-5D-3-Level, EQ-5D-5L - EQ-5D- 5-Level, NR - not reported, NA - not applicable, PwD - people with dementia

**statistically significant p<0.05*

3.4. Vignette studies

In the donanemab appraisal, the company conducted two vignette studies using time trade-off (TTO) methods with general population participants in the UK. In both studies, a pilot phase was conducted with a small number of participants (25 participants in the primary study[18] and 10 in the secondary study[20]) to ensure that the health states and methodology of the main phase were comprehensible and feasible, with participant feedback used to revise the health state descriptions. The most recent (primary) vignette study included three health states (MCI due to AD, mild AD and moderate AD) for both spouse and child caregivers in a community setting.[18, 19] The company stated that the severe health state (severe AD) was excluded from the primary study to ensure that participants were not overwhelmed by the number of TTO exercises. The second vignette study by Belger *et al*.[20] included three health states (mild AD, moderate AD and severe AD) for both caregivers living with and without patients.

Table 2 summarises the mean utility scores with standard deviations from the two vignette studies, stratified by type of caregivers (child vs spouse) and setting (community vs residential). In the primary vignette study, as reported by Matza *et al.,*[19] utility differences across all health state severity levels were statistically significant ($p<0.0001$). Additionally, utility values reported by parent caregivers were significantly higher than those reported by spouse caregivers across all health states ($p<0.0001$). In Belger *et al*., there was a statistically significant difference between most health states except the following health states:

(i) caregiver living with a patient with mild AD vs caregiver living separately from a patient mild AD,
(ii) caregiver living separately from a patient with mild AD vs caregiver living separately from a patient with moderate AD
(iii) caregiver living with a patient with moderate AD vs caregiver living separately from a patient with moderate AD, and
(iv) caregiver living with a patient with moderate AD vs caregiver living separately from a patient with severe AD.

In the company's economic model, the primary vignette study informed the utilities for (i) caregivers of people with MCI or mild dementia in both community and residential settings, and (ii) caregivers of people with moderate dementia in the community setting. Belger *et al*. informed the utility values for (i) caregivers of people with moderate dementia in the residential setting, and (ii) caregivers of people with severe dementia in both community and residential settings.

Table 2: Summary of utility scores derived from vignette studies, presented as mean (standard deviation)

	Primary vignette study[18, 19] (n=304)		Secondary vignette study by Belger *et al.*[20] (n=109)	
	Spouse in the community setting	**Child in the community setting**	**Caregiver living with a patient**	**Caregiver living separately from a patient**
MCI due to AD	**0.82 (0.18)**	**0.84 (0.18)**	NR	NR
Mild AD	**0.72 (0.25)**	**0.78 (0.20)**	0.79 (0.25)	0.74 (0.25)
Moderate AD	**0.54 (0.34)**	**0.62 (0.32)**	0.65 (0.29)	**0.71 (0.25)**
Severe AD	NR	NR	0.49 (0.30)†	**0.64 (0.32)**

AD - Alzheimer's disease; n - number of participants; NR - not reported
*Utility values directly informing the economic model are highlighted in **bold.***
The values of 0.71 and 0.64 were used for both spouse and child caregivers in the residential setting in the company's model.
The value of 0.49 was adjusted to inform the utility for severe AD in the community setting for both spouse and child caregivers.

Figure 4.1 of the NICE manual states that vignettes should be developed using the DSU's best practice recommendations from the 2020 report[1] and valued by a sample of the general population. The 2020 DSU report is titled "Measuring and valuing health-related quality of life when sufficient EQ-5D data is not available" and is authored by Rowen *et al*.[21] We note that the context of this report differs slightly from the context in which it is being applied: Rowen *et al.* are discussing a scenario in which insufficient EQ-5D are available, rather than when EQ-5D has been demonstrated to be inappropriate. Rowen *et al.* discuss two alternatives to EQ-5D: vignettes and "proxy condition" utilities – both of these are listed as options in Figure 4.1 where EQ-5D was not available from the relevant study and where values could not be identified form the literature or from statistical mapping. Figure 4.1 distinguishes between the valuation of vignettes where sufficient EQ-5D is not available and where EQ-5D is inappropriate: when EQ-5D is not available, a sample of people with the condition or the general population should complete EQ-5D based on the vignettes, whereas when EQ-5D is not appropriate, vignettes should be valued by a sample of the general population using a preference elicitation technique.

Many of Rowen *et al*.'s recommendations for vignette development are met, at least to some extent, by the two vignette studies conducted by Eli Lilly as part of their submission for donanemab. For example, the number of vignettes and health states meet the requirements of the model structure including severity and residential setting, and the vignettes use simple language, boldening to highlight differences, and they have been validated by clinicians and caregivers and refined after the pilot phase. However, the DSU is concerned that the descriptions of the vignette studies lack descriptions of some of the generic dimensions of HRQoL. Focussing only on the aspects of HRQoL that are affected by dementia caregiving

and downplaying other domains can lead to a “focussing effect” which introduces bias and leads to lower utility values. Furthermore, the vignette descriptions may encourage greater differentiation between health states than is experienced by patients/carers. This may explain why the caregiver utilities derived from the vignettes are lower than EQ-5D scores from the literature in all health states, and why the differences between health states are greater in the vignette studies. We note that even when vignettes are rigorously developed based on the best available evidence, as they are not directly provided by the caregivers of patients, they can differ from the actual health states.[22] Although vignette-based utilities may serve as a proxy for caregiver HRQoL, their consistency with values derived from preference-based measures administered to caregivers themselves remains uncertain.

Rowen *et al*. notes that vignette development is not standardised and is therefore potentially less transparent and more open to researcher influence than directly administering preference-based measures to patients/carers in a trial or observational study.[21]

3.4.1. Key concern: Vignette descriptions

The vignette health state descriptions are provided in Attachment 8 of Appendix H of Eli Lilly’s company submission for a spousal and child (caring for their parent) caregiver states for people with MCI, Mild AD and Moderate AD. The 2024 ISPOR poster authored by Matza *et al*.[19] provides an example health state for spousal carer of a person with mild cognitive impairment. The descriptions cover the following domains: information about the spouse (patient), a description of the carers’ roles or responsibilities, and the impact on the carer. Attachment 8 additionally contains information on care packages, which described the formal care that the patient receives. Here, severity is defined by MMSE: MCI: 27-28, Mild AD: 21-26, Moderate AD: 14-20.

The information about the patient includes their behaviour (for example forgetting things), their emotions (for example feelings of frustration, anxiety and depression), and their functioning (for example performing daily task and activities).

The information about the carer specifies caregiving responsibilities and lists specific tasks that the caregiver does, and ways they may try to watch or minimise the impact of the patient’s behaviour. The impact on the carer includes worrying, anxiety, feelings of irritation, disconnectedness, and in some cases fatigue/exhaustion/sleep. There is a domain for healthcare which refers to organising, attending or researching the spouses’ healthcare appointments and medication, and in some cases caregiver support groups.

Rowen *et al*. recommends that vignette descriptions include generic dimensions of HRQoL, for example the EQ-5D dimensions and descriptions, to reduce focussing effects. This ensures comparability between EQ-5D and vignette descriptions and makes vignettes more comparable across conditions. Rowen *et al.* also recommends that additional health aspects could be included as well as the EQ-5D dimensions.

The vignette descriptions for the impact on the caregiver arguably have an overlap with the EQ-5D domains for anxiety/depression and possibly usual activities, but there does not seem to be any description relating to self-care, mobility, or pain. The description of the patient also covers anxiety/depression and usual activities and possibly self-care, but not mobility or pain. There are therefore clearly some generic dimensions of HRQoL that have been omitted from the vignettes. The extent of the focussing effects and bias is unknown but is likely to have led to lower utility scores for each health state and greater differences between health states.

3.4.2. Other minor concerns

The DSU considers that using two different sources to inform the company's economic model could introduce additional uncertainty. In addition, the DSU is concerned about the comparability of results between the two vignette studies, as values for moderate AD in the Belger *et al*. are higher than those in the primary vignette study. The other minor concerns specific to each vignette study are as follows:

Minor concerns related to the primary study

Matza *et al*.[19] reports that approximately 97% of participants ranked the MCI highest and moderate AD lowest. It remains unclear to the DSU how participants who produced logically inconsistent rankings were handled; however, this is not considered likely to have meaningfully affected the mean utility scores.

The DSU considers that the company's justification for excluding severe AD state was not sufficient. The inclusion of severe AD state may have reduced some uncertainty as it remains unclear whether the two studies are directly comparable.

The protocol[18] states that "*during the screening process, reasonable efforts will be made to ensure the study sample is a representative mix of ages, genders, races, educational backgrounds, and employment statuses. Quotas will be established for employment and age categories to attempt to avoid over-representation"*. The DSU also notes that a proportion of

participants had a family member with a diagnosis of MCI or AD. However, the DSU could not identify any additional statistical analyses (e.g., subgroup comparisons) relating to this, and therefore it is unclear whether potential confounding by these variables was adequately controlled for. People whose family members have MCI or AD may value the caregiving states differently than people without experience of these conditions – if these people were overrepresented in the sample, then the overall results may not reflect the general population.

Minor concerns related to the second study by Belger et al.

Belger *et al*.[20] states that health states were first developed based on systematic literature review, review of caregiver forums, three clinical expert reviews and two caregiver and patient advocacy group representative interviews. These states were further validated by two clinical expert interviews and one caregiver interview. However, there is insufficient information regarding the detailed questionnaire used in the interviews conducted by Belger *et al*.; and therefore, the health state development by Belger *et al*. cannot be validated by the DSU. Additionally, the paper notes that the limited number of primary sources (only 2 current care partners and 1 former care partner) may lead to a depiction of caregiving that is not fully representative.

The detailed recruitment methods for both the pilot and general sample groups and the detailed demographic data are not reported in the study. The DSU was therefore unable to validate the methods and comment on the representativeness of this vignette study with respect to the caregiver populations in the UK. Additionally, the authors report that respondents over the age of 61 years were underrepresented relative to the UK population, while the proportion of participants with higher education was higher than the UK average.

3.5. Conclusion

None of the 13 studies identified in the companies' systematic literature reviews are ideal for informing the model health states because they do not separately report caregivers' HRQoL for patient severity and setting. However, these studies all report EQ-5D and are therefore aligned with NICE's preference in the manual, and they demonstrate that EQ-5D is widely used in measuring HRQoL of caregivers of people with Alzheimer's disease. It may be possible to combine estimates from different studies to populate the model health states.

The health states and settings described in the vignettes align much more closely with the model structures. However, in order to determine whether the use of vignettes is justified in this population, we need to first assess whether EQ-5D is appropriate and follow the steps of

the hierarchy in the NICE manual. The next stage (Stage 2) of the project is therefore to systematically review evidence to understand whether EQ-5D is appropriate in this population, including assessment of the studies identified by the companies and EAGs for lecanemab and donanemab.

4. STAGE 2

4.1. Introduction

The NICE manual recommends that to demonstrate EQ-5D is not appropriate requires qualitative evidence for lack of content validity for EQ-5D and systematically identified evidence that EQ-5D performs poorly on tests of construct validity (does not perform as would be expected).[1]

The companies have pointed to evidence from a handful of studies that may have examined one or more psychometric property of the EQ-5D in carers of people with AD. Examples include the correlation between change in EQ-5D and change in caregiving burden or change in time spent on specific caregiving activities in the GERAS study,[5] or the tests of known-group validity in a study by Sokolova *et al*.[23] However, these are not identified from a systematic review of available literature.

The appeal panels expressed concern about the "face validity" of the carer utility values using EQ-5D and noted that the carer utility values from Reed *et al.*[5] were "remote" from the values generated by the vignettes.[3, 4] The DSU Technical Support Document 8 (An introduction to the measurement and valuation of health for NICE submissions) describes that convergent validity can be assessed by the strength of association between EQ-5D and another measure of preferences, noting that this could come from directly administered TTO but that this test has limitations due to differences in populations. We further note that the focussing effects of the vignettes (see Section 3.4.1) limit their appropriateness for assessing the validity of the EQ-5D.

Studies do exist systematically examining the psychometric properties of EQ-5D in informal carers – for example Faller *et al* systematically reviewed the psychometric performance of generic preference-based measures including EQ-5D in informal carers (not specific to, but including evidence from, dementia or Alzeimer's Disease).[24] Faller present psychometric tests using terms such as "known-group validity", "convergent validity", "responsiveness" and "reliability". The search strategies used by Faller et al specifically include terms relating to "Psychometric" and these tests (for example validity, consistency, ceiling effects). However,

other studies of caregivers' EQ-5D, including some of the studies identified by the companies in their submissions (see Section 3) also undertake relevant analyses, but do not describe this as psychometric tests and so are not included in the review by Faller et al.[24] For example, studies may report mean EQ-5D scores for different groups of caregivers but do not describe this as "known group validity". Other studies perform regression analyses to identify statistically significant relationships between EQ-5D and other variables (for example other HRQoL measures, or measures of caregiving burden), but do not describe these correlation coefficients as "convergent validity". We considered that all of these analyses are relevant for understanding whether EQ-5D is appropriate for measuring carers' HRQoL in dementia due to Alzheimer's disease.

We aimed to systematically examine the appropriateness of EQ-5D in a population of carers of people with cognitive impairment or dementia due to Alzheimer's disease.

4.2. Methods

We conducted a systematic literature review to understand how the EQ-5D is affected by caregiving for people with cognitive impairment or dementia due to Alzheimer's disease. We aimed to identify studies that analysed either differences in EQ-5D between caregivers with different experiences of caregiving, or how EQ-5D changed as other variables changed (for example patient disease severity, caregiving burden, care setting). We were not looking for studies that would necessarily be used to populate the model structures discussed in Section 3, but for studies that helped us understand whether EQ-5D is appropriate in this population.

We developed a search strategy with the aim of systematically and pragmatically identifying relevant studies within the time frame and resources available, searching up until April 2026. We already had the 13 studies identified by the two companies in their submissions, both of which used systematic literature reviews until 2022/2023. We looked specifically for studies that reported EQ-5D of carers in Alzheimer's disease or dementia, published since database inception – this was to identify studies that contained information useful for understanding the relationship between the EQ-5D of people caring for someone with Alzheimer's Disease and other variables, noting that some of these may have been excluded by the companies as not relevant for populating their models. We supplemented this with searches for broader HRQoL terms for carers in Alzheimer's disease or dementia, published since 2022, to update the companies' systematic reviews. These broader search terms additionally identify studies that may have included EQ-5D but did not report this in the abstract or title. The search strategy is included as an Sppendix in Section 8.1.

We applied the same pragmatic and systematic approach to our inclusion and exclusion criteria, aiming to include all relevant studies and exclude studies which were not useful for answering our research question. We included studies where informal/unpaid/family caregivers of people with cognitive impairment or dementia due to Alzheimer's disease reported their own HRQoL. We excluded studies where caregivers proxy-reported patients' HRQoL, studies that measured HRQoL of formal/paid carers, and studies of carers in other populations (for example Parkinson's). We included EQ-5D 3L and 5L versions using any value set, and excluded EQ visual analogue score (VAS), EQ-HWBS, and any other HRQoL measures (such as SF-6D, HUI, Carer quality of life [CarerQoL]). We included cross-sectional and longitudinal studies that analysed caregivers' HRQoL, either by reporting differences in EQ-5D scores or change in EQ-5D by groups, or by regression analyses. We excluded studies that only reported mean EQ-5D scores for caregivers as one group, and studies that only compared caregivers to non-caregivers, since these are not useful for understanding determinants of carer's EQ-5D scores. We excluded interventional studies (for example randomised controlled trials) since these tend to be confounded by or focus on the effect of an intervention on carers' EQ-5D, and these are not necessarily transferable to the lecanemab and donanemab appraisals. We excluded systematic reviews and economic evaluations since these used already published values, preferring to find the original studies ourselves. We included studies from any country but excluded studies that were not in English due to the time and resources that would be required to translate them. We included full text original articles, and we included conference abstracts unless the work had since been published as a full text paper (to avoid double counting the same studies). Inclusion and exclusion criteria are shown in Table 3.

We excluded three of the 13 studies identified by the company in accordance with our inclusion/exclusion criteria: the study by Woods *et al* was an interventional study,[6] the study by Dixit *et al.* was in a population with young onset dementia,[11] and the study by Fang *et al.* did not perform any statistical tests to analyse differences in carers' EQ-5D.[13]

Due to time and resource constraints, one reviewer screened and extracted data from all records. A second reviewer screened a sample (10%) of titles and abstracts to check both reviewers agreed on inclusion and exclusion decisions.

Table 3: Inclusion and exclusion criteria

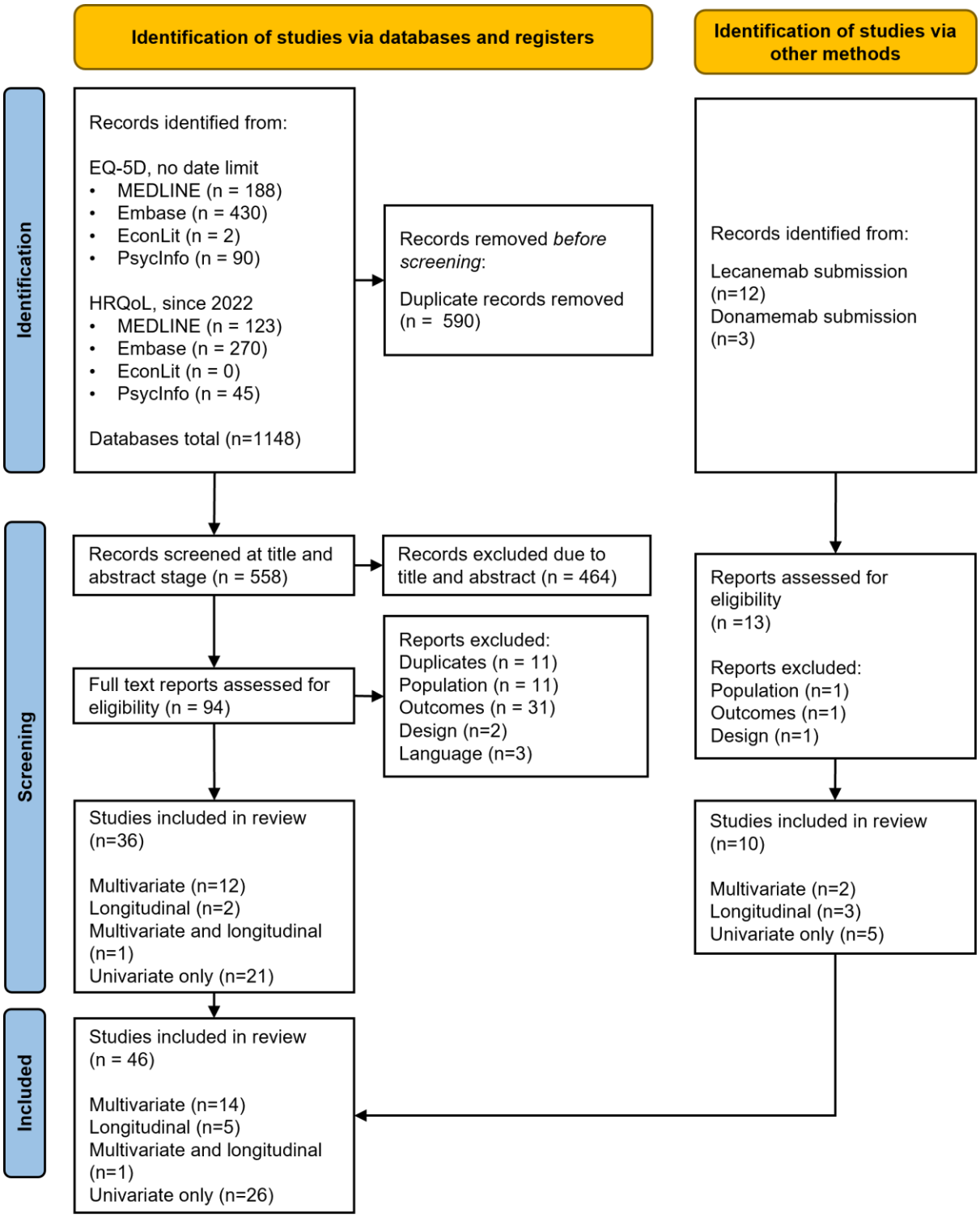
	Include	**Exclude**
Population	Informal, unpaid or family caregivers of adults with cognitive impairment, dementia and/or AD Informal caregivers of patients living in community or residential care home/long-term care institute Informal, unpaid or family caregivers of adults with a mix of different health conditions including cognitive impairment, dementia and/or AD	Formal / paid care workers Healthcare staff People with AD Caregivers of patients with health conditions not including dementia due to AD (e.g. Parkinsons, Huntingdon's, young onset dementia, Lewy body dementia, stroke-related dementia) Caregivers of patients exclusively with specific complications of dementia (e.g. hearing difficulties, sleep disturbance) Caregiver's proxy reporting of patients' health-related quality of life
Outcome	Caregiver's health-related quality of life measured using EQ-5D (3L or 5L) index score, anchored 0-1 or clearly rescaled (e.g. 0-100). Caregiver's EQ-5D must be analysed by patient or caregiving variables, with tests of significance or confidence intervals reported.	EQ-5D VAS. EQHWB. Other measures of HRQoL. EQ-5D scores of whole caregiver population, or for caregivers vs non caregivers. EQ-5D scores by intervention. EQ-5D domain scores only.
Study design	Cross-sectional or longitudinal studies of caregiving populations.	Systematic reviews Network meta-analyses Economic evaluations that use published HRQoL data Experimental/interventional / trials Study protocols
Language	English	Other than English
Country	Any	Not applicable
Publication type	Full-text original articles and abstracts from conferences	Editorials, newspaper articles, book sections, letter, expert opinion or commentary and reviews. Conference abstracts where the full text publication has since been published.

AD - Alzheimer's disease; EQ-5D VAS - *EQ-5D Visual Analogue Scale; EQHWB - EQ Health and Wellbeing; HRQoL - health-related quality of life*

4.3. Results

The PRISMA diagram is shown in Figure 1.

Figure 1: PRISMA diagram



4.3.1. Included studies and analyses presented

Most (40 of 46) of the included studies measured carers' EQ-5D and other variables at one time point (cross-sectional studies). Many (26 of 40) of these studies analysed the relationship between carers' EQ-5D and one variable at a time (often described as "univariable" or "univariate" analysis, or as "bivariate" analysis to determine the relationship between carers' EQ-5D and one other variable). While this analysis tells us something about the relationship between carers' EQ-5D and that variable, it does not account for other factors that may also affect the relationship between carers' EQ-5D and individual variables (confounding). For example, there might be a relationship between spousal carers' EQ-5D and the age of the person they care for – but spousal carers of older patients are themselves more likely to be older, so the age of the carer confounds this relationship.

We were therefore particularly interested in studies that attempted to control for other variables – this could either be through multivariate analysis (which adjusts for multiple variables at the same time) of cross-sectional data or through longitudinal analysis studying whether changes in carer's EQ-5D are correlated with changes in other variables (assuming that the other potential confounding variables do not also change). The 26 studies which only report univariate analyses are described in Table 12 in the Appendix in Section 8.3.

Table 4 summarises the 20 studies that report multivariate and/or longitudinal analyses.

All studies used EQ-5D, but some used the 3L version whereas others used 5L (in some cases cross-walked/mapped to 3L), and we note previous research suggests carer utilities will generally be higher with 5L, but disutilities associated with health conditions[25] or caring[26] will be smaller with 5L. Furthermore, the studies use a mix of value sets, with many using the UK value set, some non-UK studies using country-specific value sets, and others not reporting the value set used. These two factors limit the comparability of outcomes between studies, but all studies are relevant for answering the research question of whether EQ-5D is appropriate in measuring HRQoL of carers in Alzheimer's disease.

We included studies within and beyond the UK, with no limit on geography. We recognise that UK-specific studies may be most relevant for informing what the average EQ-5D score is for carers of people with Alzheimer's Disease in the UK, particularly when considering the differences in health and social care provision across countries, as well as societal norms and cultural expectations in unpaid caregiving. However, we believe that all these studies are potentially useful for answering our research questions, since the multivariate analyses allow us to isolate the effects on carers' HRQoL of specific aspects of patient disease or caregiving factors.

The definition of caregiver varies between studies and is often not reported. It is therefore unclear how comparable studies are, and whether the caregiver included is the primary carer in most studies (one study did define the carer as the primary caregiver[5]). One study reported whether there were other people involved[27] but did not adjust for this. In many studies, the carers are mostly the patient's spouse, but this is not always the case, and some studies do not report the relationship between carer and patient.

The studies are from a mix of care settings, with some conducted exclusively in the community, some a mix of community and care homes, some specifically studying the transition from community to care home, and some not reporting the setting. Furthermore, only two studies reported the level of formal care received at home [28, 29] – of these, one used the level of formal care to define patient severity[29] and the other found that formal care was not significant in univariate analysis and so did not include it in the multivariate analysis.[28]

The differences in the study populations and settings (and lack of clarity on these factors in some studies) limit the comparability of findings. We consider they are all potentially valuable in deepening our understanding, but do not make attempts to formally combine results (for example using meta-analysis) due to differences in population, design and outcomes.

Table 4: Summary of studies

Study	HRQoL measure 3L or 5L + value set?	Caregivers' characteristics				Care setting	Definition of caregiver	Patient severity inclusion criteria	Study design	Analysis	Country
		Sample size	Number (%) of females	Mean age (SD)	Caregiver's relationship to patient (%)						
Black 2018[9]	EQ-5D-3L, value set NR	Overall = 1201 Included in regression analysis = 898	829 (69.1%)	63.9 (13.7)	Partner/ spouse: 56.8%,	Living with patient: 75.8% Community / institution: NR	Accompanying the patient to their consultation	Diagnosis of early cognitive impairment or AD	Cross-sectional*	Multivariate regression	France, Germany, Italy, Spain, UK, and US
Farina 2020[12]	EQ-5D-3L, country-specific value set (UK)	377	202 (64.7%)	69.2 (11.45)	Spouse: 64.7%	Living with patient: 53.8% Care-home: 16.7%	Self-identify themselves as a carer for the person with dementia,	Medical diagnosis of dementia 60.7% AD Average sMMSE 14.9 (9.08)	Cross-sectional	Multivariate regression	UK
Chekani 2021[30]	EQ-5D-3L, value set NR	1357	NR	NR	NR	Nursing home: NR Community: NR	NR	Based on physician's perception of dementia severity	Cross-sectional*	Multivariate regression	France, Germany, Italy, Spain, UK and US

Study	HRQoL measure 3L or 5L + value set?	Caregivers' characteristics				Care setting	Definition of caregiver	Patient severity inclusion criteria	Study design	Analysis	Country
		Sample size	Number (%) of females	Mean age (SD)	Caregiver's relationship to patient (%)						
Park 2018[31]	EQ-5D-3L, country-specific value set (UK)	Baseline: 1020 6 mth: 569 12 mth: 452 24 mth: 187	452 (69.2%)	67.9 (12.8)	Spouse: 69.9%	Living with patients: 75.8%	NR	Patients in memory assessment services with dementia, MCI, or no diagnosis (based on patient's case notes)	Longitudinal	Multivariate regression	UK
Shinagawa 2026[32]	EQ-5D-5L with Japanese population values	705	304 (43.1%)	54.6 (11.5)	Spouse: 5.5%	Living with family member	Primary or partial caregiver	Patient with AD	Cross-sectional web-based survey	Multivariate regression	Japan
Ohno 2026[33]	EQ-5D-5L, value set unclear	805	418 (51.9%)	NR. 36.8% >=65	NR	395/677 in community, 282/677 in assisted	Currently caring for adult relative	Patients with AD/dementia	Cross-sectional	Pairwise comparison and generalised	Japan

Study	HRQoL measure 3L or 5L + value set?	Caregivers' characteristics				Care setting	Definition of caregiver	Patient severity inclusion criteria	Study design	Analysis	Country
		Sample size	Number (%) of females	Mean age (SD)	Caregiver's relationship to patient (%)						
						living/institution.				linear models	
Montgomery 2018[29]	EQ-5D-3L, country-specific value set (Japan)	300	135 (45.0%)	53.89 (11.02)	Married: 62.3%	Community	An adult caring for an individual diagnosed with AD dementia and not receiving payment for caregiving duties	Severity based on LTCI scores	Cross-sectional	Both bivariate and multivariate regression	Japan
Majoni 2017[34]	EQ-5D-3L, Canadian value set	200	130 (65%)	71 (NR)	NR	Community: 92% Institution: 8%	Primary informal caregiver	Mild or moderate AD	Cross-sectional	Regression with multiple imputation	Canada
Lee 2025[28]	EQ-5D-5L, value set NR	130	92 (70.8)	66.83 (13.4)	Spouse: 54.6%	Community	NR	Level 4 (mild dementia) and level 5 or above (moderate to severe dementia) based on	Cross-sectional	Multivariate regression	Australia

Study	HRQoL measure 3L or 5L + value set?	Caregivers' characteristics				Care setting	Definition of caregiver	Patient severity inclusion criteria	Study design	Analysis	Country
		Sample size	Number (%) of females	Mean age (SD)	Caregiver's relationship to patient (%)						
								the GDRS.			
Haikio 2020[35]	EQ-5D-3L, used the UK time trade-off-based index values	188	134 (71%)	60 yr (25 to 84)	NR	Living in urban area: 87%	A family member, neighbour or friend who, carries out tasks of a supportive nature that go beyond normal relationships of reciprocity among adults†	Mild and severe dementia based on Norwegian translation of the Berger Dementia Scale (BDS)	Cross-sectional	Both bivariate and multivariate regression	Norway
Dixon 2006[36]	EQ-5D-3L, value set NR	64	59%	63 (SD NR)	Spouse: 52%	NR	NR	Dementia diagnosis was categorised using three-digit ICD codes (10th revision). Severity of	Cross-sectional	Multivariate regression	UK

Study	HRQoL measure 3L or 5L + value set?	Caregivers' characteristics				Care setting	Definition of caregiver	Patient severity inclusion criteria	Study design	Analysis	Country
		Sample size	Number (%) of females	Mean age (SD)	Caregiver's relationship to patient (%)						
								dementia was not reported.			
Clarke 2021[37]	EQ-5D-3L	1,283	(68.7%)	69.3 (NR)	Spouse: 47.4%	Community (memory services/ clinics)	Primary family carers	Dementia (55.7% Alzheimer's disease)	Cross-sectional	Multiple regression models	UK
Monin 2020[38]	EQ-5D-3L, Dutch tariff	521	348 (66.8%)	64.6 (12.5)	Spouse: 25.5%	Community: 97.4%, Living in elderly home: 2.6%	Primary informal caregivers	Established/formal diagnosis of dementia	Cross-sectional	Actor Partner Interdependence Model	Netherlands
Kim 2022[39]	EQ-5D-3L, Korean version	229	143 (62.5%)	NR. 52.0% aged 75-84.	Spouses (all)	Community	Primary caregiver	Patient diagnosed with dementia, mild dementia excluded	Cross-sectional	Pearson's or Spearman's correlation, and regression models	Korea
Oremus 2012 (abstract only)[40]	EQ-5D-5L, value set NR	216	65.74%	Median age: 69	NR	Community: NR Institutions: NR	NR	NR	Cross-sectional	Multivariate regression	Canada

Study	HRQoL measure 3L or 5L + value set?	Caregivers' characteristics				Care setting	Definition of caregiver	Patient severity inclusion criteria	Study design	Analysis	Country
		Sample size	Number (%) of females	Mean age (SD)	Caregiver's relationship to patient (%)						
Reed 2017[5]	EQ-5D-3L (country-specific value set+)	1495	958 (64.2%)	67.3 (12.0)	Spouse: 65.9%	Living with patient (community dwelling): 76%	Primary caregiver, responsible for the patient for at least 6 months per year	Mild, moderate and severe AD based on MMSE scores	Observational study	Spearman's rank correlation	France, Germany and UK
McLoughlin 2020δ[27]	EQ-5D-5L, value set NR	576	65%	62 (11)	Spouse: 35%	Living with patient: 46%	NR	NR	Longitudinal‡	Spearman's rank correlation Cohen's d	UK
Bradshaw 2013[7]	EQ-5D, value set NR	Baseline: 180 At 6 mth: 100	66%	62 (IQR: 56 to 73)	Spouse: 24%	Baseline: community: 129 care home: 51	Someone who has regular contact with the patient participant for at least an hour a week	Mild, moderate and severe CI based on MMSE	Longitudinal	Chi-squared tests and Kruskal–Wallis tests	UK
Bleijlevens 2015[8]	EQ-5D-3L, value set NR	Overall: 2014 ILTC: 791 home care	ILTC: 65.4% HC: 68.8%	ILTC: 61.1(11.1) HC: 64.7(13.4)	Spouse (ILTC): 18.4% Spouse (HC): 41.7%	ILTC and HC	spouses/ partners, other members of the household, relatives,	Receiving formal care at home but deemed at risk of admission	Prospective cohort study	Independent sample t-tests or chi-square tests	Estonia, England, Sweden, Spain, France, German

Study	HRQoL measure 3L or 5L + value set?	Caregivers' characteristics				Care setting	Definition of caregiver	Patient severity inclusion criteria	Study design	Analysis	Country
		Sample size	Number (%) of females	Mean age (SD)	Caregiver's relationship to patient (%)						
		(HC): 1223					friends, neighbours or others; visited the PwD at least twice a month	as judged by a professional caregiver			y, the Netherlands
Vroomen 2016 (abstract only)[41]	EQ-5D, value set NR	521	NR	NR	NR	Living independent or living together with the informal caregiver or nursing home: NR	NR	NR	Longitudinal	Repeated measures ANCOVA	NR

AD - Alzheimer's disease; ANCOVA - Analysis of Covariance; BDS - Berger Dementia Scale; CI - cognitive impairment; EQ-5D-3L - EQ-5D - 3- levels; EQ-5D-5L - EQ-5D- 5- levels; GDRS - Global Deterioration Scale; HC - home care; HRQOL - health-related quality of life; ICD - International Classification of Diseases; ILTC - institutional long-term care; LTCI - long-term care institution; MMSE - Mini-Mental State Examination; NR - not reported; PwD - people with dementia; SD - standard deviation

**Real world data. 2015/16 Adelphi Real World Dementia Disease Specific Programme (DSP)™*

†any family carer to a person above 65 years of age with suspected, or diagnosed dementia, or symptoms of age-related memory loss. The care recipient could be living independently, in a nursing home facility, or in the same household as the carer.

‡ via 3 waves of Family Resources Survey across the UK (excluding Northern Ireland) in 2013-2014, 2014-2015 and 2015-2016

δsample also includes carers of patients with other non-AD conditions

4.3.2. Multivariate analyses

Fifteen studies presented multivariate analyses. The analyses presented, and whether they were statistically significantly associated with carers' EQ-5D are summarised in Table 6. Where multiple studies analysed the effect of the same/similar variables on carers' EQ-5D, the effect sizes are presented in Table 7. In studies that adjusted for other factors (listed in Table 5) that potentially affect carers' EQ-5D, we found:

- Four studies looked at the caregiving burden as a predictor of carers' EQ-5D, all of which found statistically significant relationships in at least one time point.[12, 28, 31, 36] Three of these studies used ZBI,[12, 28, 31] and one used the domain of CDQLP described as relevant.[36] One study used ZBI at multiple time points and found a statistically significant relationship in 3 of 4 time points.[31] The direction of the relationship is negative: as the caregiving burden increased, carers' EQ-5D decreased.
- Five studies looked at patient severity as a predictor of carers' EQ-5D, with mixed findings.[9, 12, 29, 30, 35] They used different measures/classification for patient severity. Three studies found that carer's EQ-5D was statistically significantly associated with some,[9, 29, 30] but not all, differences in patient severity – in these cases, as patient severity increased, carers' EQ-5D decreased. Two studies found no significant association between carers' EQ-5D and patient severity.[12, 35]
- Five studies looked at the relationship between carers' EQ-5D and patient's dementia symptoms or needs, with mixed findings.[12, 30, 32, 34, 38] Three studies found that carers' EQ-5D was statistically significantly associated with dementia symptoms/needs (using agitation/aggression and related symptoms (AARS),[30] behavioral and psychological symptoms of dementia (BPSD),[32] patient-reported unmet needs [38]). One of these found no significant association between carers' EQ-5D and the carers' proxy report of the patient's unmet care needs.[38] Two studies found no significant association between carers' EQ-5D and dementia behaviour disturbance scale,[34] and neuropsychiatric Inventory (NPI).[12]
- Three studies looked at patient HRQoL as a predictor of carers' EQ-5D, with mixed findings.[12, 36, 40] One study reported that carers' EQ-5D was statistically significantly associated with carer-reported DEMQOL proxy for patients.[12] One study reported that carers' EQ-5D was statistically significantly associated with the patient's proxy-reported EQ-5D pain domain, but not other domains of proxy-reported EQ-5D for patients.[36] One study reported that carers' EQ-5D was not statistically significantly associated with patient-reported EQ-5D.[40]

- Two studies looked at duration of caring as a predictor of carers' EQ-5D and found it was not statistically significant.[29, 36]
- Five other studies considered other variables.[33, 35, 39 29, 37] Four found carers' EQ-5D was significantly associated with: patient's cancer diagnosis,[33] carers' health literacy,[35] care-recipient dependence scale, carer stress scale and carer role captivity scale,[37] stress status, depression and sleep quality.[39] One found some significant and some non-significant associations between care provision time and carers' EQ-5D.[29]
- Two studies looked at the relationship between whether the patient lived at home or in a nursing/care home and carers' EQ-5D.[12, 30] One study did not find a statistically significant difference.[12] One found that carers' EQ-5D was statistically significantly higher for carers where the patient lived in a nursing home.[30]

Table 5: Adjusted variables across included studies

Study	Patient dementia outcome / severity	Carer health	Carer-patient relationship	Caregiver employment	Country / region	Caregiving burden	Patient HRQoL	Setting (care home / community)	Patient demographics	Carer Ethnicity	Carer Marital status	Carer Education	Income / deprivation / insurance
Black 2018[9]	y	y	y	y	y								
Farina 2020[12]	y		y			y	y	y					
Chekani 2021[30]	y				y			y	y				
Park 2018[31]			y				y			y			y
Shinagawa 2026[32]									y				y
Ohno 2021[33]				y							y		y
Montgomery 2018[29]	y		y	y		y			y		y		
Majoni 2017[34]	y		y	y								y	y
Lee 2025[28]	y	y	y	y		y						y	
Haikio 2020[35]	y	y			y					y		y	
Dixon 2006[36]							y		y				

Study	Patient dementia outcome / severity	Carer health	Carer-patient relationship	Caregiver employment	Country / region	Caregiving burden	Patient HRQoL	Setting (care home / community)	Patient demographics	Carer Ethnicity	Carer Marital status	Carer Education	Income / deprivation / insurance
Clarke 2021[37]	y	y	y	y									
Monin 2020[38]	y	y	y						y				
Kim 2022[39]		y		y	y							y	
Oremus 2012 (abstract only)[40]	Y		y	y					y				

HRQOL - health-related quality of life; y - yes; Blank - not analysed
All adjusted for carer age and sex

Table 6: Statistically significant associations between carers' EQ-5D and other variables in multivariate analyses

Study	Care setting	Patient severity	Patient symptoms	Patient HRQoL	Duration of caring	Caregiver burden	Other
Black 2018[9]		MMSE Mild vs prodormal: N Moderate vs mild: Y Severe vs moderate: N					
Farina 2020[12]	N	MMSE: N	NPI: N	DemQOL Proxy: Y		ZBI-22 item: Y	
Chekani 2021[30]	Y	Moderate vs mild: Y Severe vs mild: N (physician's perception)	AARS: Y				
Park 2018[31]						ZBI-12 item: Baseline: Y 6 months: Y 12 months: Y 24 months: N	
Shinagawa 2026[32]			BPSD: Y				

Study	Care setting	Patient severity	Patient symptoms	Patient HRQoL	Duration of caring	Caregiver burden	Other
Ohno 2021[33]							Patient also has cancer: Y
Montgomery 2018[29]		Nursing care level certification severity: High vs low: Y Medium vs low: N			N		% caregiver: N % nurse: Y Total: N
Majoni 2017[34]			Dementia behaviour disturbance scale: N				
Lee 2025[28]						ZBI 22-item: Y	
Haikio 2020[35]		Berger dementia scale. Mild vs severe: N					Health literacy: Y
Dixon 2006[36]				Pain domain EQ-5D: Y Other domains EQ-5D : N	N	relevant domain of CDQLP: Y	

Study	Care setting	Patient severity	Patient symptoms	Patient HRQoL	Duration of caring	Caregiver burden	Other
Clarke 2021[37]							Care-recipient dependence scale: Y Relative stress scale: Y Role captivity scale: Y
Monin 2020[38]			Patient-reported unmet needs (CANE): Y Carer proxy-reported patient unmet needs (CANE): N				
Kim 2022[39]							Stress status: Y Caregiver depression: Y Caregiver sleep quality: Y
Oremus 2012 (abstract only)*[40]				Patient-reported EQ-5D: N			

AARS - agitation/aggression and related symptoms; BPSD - behavioral and psychological symptoms of dementia; CANE - Camberwell Assessment of Need for the Elderly; CDQLP - Community Dementia Quality-of-Life Profile; DemQOL - Dementia quality of life; HRQOL - health-related quality of life; MMSE - Mini-Mental State Examination; NPI - Neuropsychiatric Inventory; ZBI - Zarit Burden Interview
*Y - yes; N - no; Blank - not analysed, *Abstract available only (conference proceeding)*

Table 7 Multivariate effect sizes

Study	Care setting	Patient severity	Patient HRQoL	Duration of caring	Caregiver burden
Black 2018[9]		MMSE: Mild vs prodromal: -0.018 (-0.064 to 0.027) **Moderate vs mild:** **-0.033 (-0.057 to -0.009)** Severe vs moderate: -0.02 (-0.062 to 0.022)			
Farina 2020[12]	Care home: -0.05 (-0.13 to 0.03, p=0.19)	MMSE: -0.00 (-0.01 to 0.00, p=0.19)	**DemQOL Proxy:** **0.00 (0.00 to 0.01, p=0.03)**		**ZBI 22 item:** **--0.01 (-0.01 to -0.00) (p<0.001)**
Chekani 2021[30]	**Nursing home: 0.09 (0.06 to 0.12, p<0.001)**	Physicians' perception **Moderate vs mild: -0.03 (-0.06 to -0.01, p=0.006)** Severe vs mild: -0.02 (-0.05 to 0.01, p=0.212)			
Park 2018[31]					ZBI 12 item: **Baseline:** **-0.006 (-0.009 to –0.004)**

Study	Care setting	Patient severity	Patient HRQoL	Duration of caring	Caregiver burden
					6 months: -0.004 (-0.007 to -0.002) **12 months: -0.006 (-0.009 to -0.003)** 24 months: -0.002 (-0.007 to 0.003)
Montgomery 2018[29]		Nursing care level certification severity: **High vs low: -0.122 (-0.211 to -0.034, p=0.007)** Medium vs low: -0.031 (-0.105 to 0.043, p=0.414)		2-4 years vs 2: 0.001 (-0.098 to 0.100, p=0.984) 4-6 years vs 2: 0.030 (-0.075 to 0.135, p=0.573) 6+ years vs 2: 0.025 (-0.079 to 0.130, p=0.634) Can't recall vs 2: 0.002(-0.121 to 0.125, p=0.972)	
Lee 2025[28]					**ZBI 22-item:** **-0.01 (-0.01 to -0.002, p=0.001)**
Haikio 2020[35]		Berger dementia scale.			

Study	Care setting	Patient severity	Patient HRQoL	Duration of caring	Caregiver burden
		Mild vs severe: -0.004 (-0.06 to 0.05, p=0.90)			
Dixon 2006[36]			Proxy reported **Severe vs no pain: -0.45 (p=0.02)** Some vs no pain: -0.07 (p=0.34)	Duration of care: -0.001 (p=0.41)	**CDQLP carer score:** **-0.00, p=0.04**
Oremus 2012 (abstract only)*[40]			Patient-reported EQ-5D: 0.1086 (-0.0248 to 0.2420)		

AARS - agitation/aggression and related symptoms; BPSD - behavioral and psychological symptoms of dementia; CANE - Camberwell Assessment of Need for the Elderly; CDQLP - Community Dementia Quality-of-Life Profile; DemQOL - Dementia quality of life; HRQOL - health-related quality of life; MMSE - Mini-Mental State Examination; NPI - Neuropsychiatric Inventory; ZBI - Zarit Burden Interview; Blank - not analysed
**Abstract available only (conference proceeding)*
Bold text = statistically significant at 5% level

4.3.3. Longitudinal analyses

Six studies presented longitudinal analyses. The analyses presented, and whether they were statistically significantly associated with changes carers' EQ-5D are reported in Table 8.

Reed *et al*. 2017[5] analysed the correlation between change in 928 Alzheimer's carers' EQ-5D from baseline to 18 months, and change in ZBI from baseline to 18 months. They found that this correlation (-0.09) was statistically significant (p=0.006) and described it as "very weak." They found no statistically significant correlation between carer's EQ-5D change and change in T-IADL (time spent on instrumental activities of daily living, for example cooking and shopping).

Park *et al*. 2018[31] analysed longitudinal associations from baseline between carer's EQ-5D and ZBI-12 item and between carers' EQ-5D and patients' DEMQOL, at 6 months (n=485), 12 months (n=398) and 18 months (n=169). Carers and patients were recruited after their first appointment at a memory assessment service. Park *et al*. found that there was a statistically significant and negative relationship between change in ZBI score and change in EQ-5D score at 12 months (one unit increase in ZBI score was associated with a reduction of 0.005 in EQ-5D). The relationship between EQ-5D and ZBI were not statistically significant at 6 or 18 months. The relationship between carers' EQ-5D and patients' self-reported DEMQOL was not statistically significant at 6, 12 or 18 months.

McLoughlin *et al*. 2020[27] analysed the responsiveness of carers' EQ-5D to changes in patients' EQ-5D (proxy-reported by carers) and changes in the number of caring hours over 12 months. They included 155 carers of patients with dementia, 89 with stroke, 144 with mental illness and 126 with rheumatoid arthritis. Longitudinal associations are only reported for all groups combined (including non-dementia patients), where responses from follow-up were available. They calculated effect sizes and assessed them using Cohen's d. They found that the effect size was small where patient's EQ-5D improved or did not change, and moderate where patients' EQ-5D worsened (total n = 264). They found that the effect size was small where the number of hours of care decreased, increased or stayed the same, using thresholds of 20 and 50 hours per week (total n = 293).

From these three studies, there is mixed evidence of whether EQ-5D is responsive to changes in patients' HRQoL, and changes in caregiving burden (measured by ZBI or hours/week). The longitudinal associations between these outcomes were statistically significant in some cases, and usually described as weak, small or moderate.

Three studies looked at the change in carers' EQ-5D when patients transitioned to long-term care (nursing home/institution).[7, 8, 41] Two found no statistically significant differences in carers' EQ-5D after patient transition (Bradshaw *et al.* 2013[7] and Bleijlevens *et al*. 2015[8]). One study found carers' EQ-5D was statistically significantly worse at six months, but not statistically significant different at 12 months (Vroomen *et al*. 2016).[41]

Table 8: Statistically significant associations between change in carers' EQ-5D and change in other variables in longitudinal analyses

Study	ZBI	T-IADL	Patient quality of life	Hours of care	Patient moves to long term care
Reed 2017[5]	Correlation between change scores baseline to 18 month: **-0.09 (-0.15 to -0.03)**	Correlation between change scores baseline to 18 month: 0.03 (-0.04 to 0.008)			
Park 2018[31]	Adjusted difference in change Baseline to… 6 month: N 12 month: Y 24 month: N 6 month: -0.001 (-0.005 to 0.003) **12 month: -0.005 (-0.008 to -0.0007)** 24 month: -0.002 (-0.007 to 0.0063)		DEMQOL (patient-reported): Baseline to… 6 month: -0.0006 (-0.002 to 0.001) 12 month: 0.0004 (-0.001 to 0.002) 24 month: 0.0008 (-0.003 to 0.005)		
McLoughlin* 2020[27]			EQ-5D (proxy) Standardised response mean: **Improved: -0.26** **No change: -0.28**	20/50 per week threshold: Standardised response mean: **Less hours: -0.20**	

			Worsened: -0.54	**No change: -0.36** **More hours: -0.45**	
Bradshaw 2013*[7]					Median EQ-5D change (IQR): 0 (-0.09 to 0.16)
Bleijlevens 2015[8]					Mean EQ-5D at baseline vs follow-up: 0.77 vs 0.77
Vroomen 2016 (abstract only)[41]					6 month: p=0.016 12 month: not significant

DEMQOL - Dementia quality of life; IQR - interquartile range; T-IADL - time spent on instrumental activities of daily living; Y - yes; ZBI - Zarit Burden Interview
Y - yes; N - no; Blank - not analysed
**sample also includes carers of patients with other non-AD conditions*
Bold = significant at 5% level

4.3.4. Overall evidence

Altogether, we identified 15 studies that reported multivariate analysis, and 6 studies that reported longitudinal associations. One study (Park *et al*. 2018) reported both, so there is a total of 20 studies. Considering together the evidence from the 20 studies:

- Six of six studies found that increasing caregiver burden decreased carers' EQ-5D, [5, 12, 27, 28, 31, 36] (noting results at some time points are not significant within one study, and correlations are often weak). Using ZBI (four studies), an increase of 1 point on the 0-88 ZBI scale decreased carers' EQ-5D by 0.01, and an increase of 1 point on the 0-48 ZBI scale decreased carers' EQ-5D in the range 0.002 to 0.006
- Two of two studies found a statistically significant relationship between carer's EQ-5D and carer's proxy-reported patient HRQoL (one study using DEMQOL, one using EQ-5D).[12, 27] One additional study found a relationship between carers' EQ-5D and proxy reported patient EQ-5D pain domain, but not the other domains.[36]
- Two of two studies did not find a statistically significant relationship between carer's EQ-5D and patient-reported patient HRQoL (one study using DEMQOL, one using EQ-5D).[31, 42]
- Three of five studies found some statistically significant relationships between patient severity and carers' EQ-5D, with increasing severity associated with worse carers' EQ-5D[9, 30 29] but each of these also found some changes in patient severity were not statistically significantly associated with carers' EQ-5D. Two studies found no statistically significant relationships between patient severity and carers' EQ-5D.[12, 35]
- Three of five studies found no statistically significant relationships between whether the patient lived at home or in a nursing/care home and carers' EQ-5D.[7, 8, 12] One study found that carers' EQ-5D was statistically significantly higher for carers where the patient lived in a nursing home.[30] One study found that carers' EQ-5D was statistically significantly higher within six months of patient admission to a nursing home, but no statistically significant differences within 12 months.[38]
- Two of two studies found no statistically significant relationships between carers' EQ-5D and duration of caring.[29, 36]

4.3.4.1. Patient's HRQoL as a predictor of carers' EQ-5D

The evidence suggests that patient-reported HRQoL is unrelated to carers' EQ-5D scores, but that there is evidence of a relationship between carers' own EQ-5D scores and carer-reported patient HRQoL scores (or specific domains) for patients. It is perhaps unsurprising that there is a correlation between carers' self-reported and proxy-for-patient EQ-5D scores, and there is potential for double-counting the impact of AD on patient and family if the carer is

considering the impact on themselves while proxy-reporting the patient's HRQoL.[43] We note that the lecanemab and donanemab economic models use patient-reported EQ-5D for the MCI and mild states, and proxy-reported values for the moderate and severe states.[44, 45]The patient EQ-5D scores are confidential and are not reported here, but we would generally expect patient HRQoL scores to worsen (be lower) in more severe health states, and that carer HRQoL scores would change in the same direction. Previous research across health conditions has found that carers' HRQoL is statistically significantly correlated with patient's HRQoL, but also with some measure of how much care is provided,[46-48] suggesting that patient's HRQoL is not the only determinant of carers' HRQoL.

4.3.4.2. Caregiver burden as a predictor of carers' EQ-5D

The systematic review indicates that increased caregiving burden is consistently and statistically significantly associated with decreased carers' EQ-5D. The direction of this effect is as expected, but the correlation between change in EQ-5D and change in ZBI is weak or very weak. The ZBI is a measure of caregiving burden, and there are different versions. The 22 item ZBI is scored 0-88, and the scoring system suggests that scores of 0-20 indicate no to mild burden, scores of 21-40 indicate mild to moderate burden, scores of 41-60 indicate moderate to severe burden, and scores above 60 indicate a severe burden. The studies indicate an effect size for ZBI-22 item of approximately 0.01[12, 28] (noting this is an upper bound due to rounding, and confidence intervals indicate a range from 0.00 to 0.01, suggesting that the coefficient is likely below 0.01): increasing ZBI by 1 point would decrease EQ-5D by 0.01. The 12 item ZBI is scored 0-48, and the scoring system suggests that scores of 0-10 indicate no to mild burden, scores of 11-20 indicate mild to moderate burden, scores, and scores above 20 indicate a high burden. The studies indicate an effect size for ZBI-12 item in the range of 0.002 to 0.006: increasing ZBI by 1 point would decrease EQ-5D by between 0.002 and 0.006.

We have estimated the associated disutility for these ZBI-12 item and ZBI-22 item ranges assuming all other determinants of carers' HRQoL remain constant. We note that the range of ZBI and EQ-5D scores used to estimate the relationships in the included studies do not span the whole range of ZBI, so we are extrapolating beyond the data used to establish these relationships and the linear assumption may not hold. However, we suggest this is useful for understanding how carers' EQ-5D would be expected to change as caregiving burden increased.

In Table 9, we have used the minimum, maximum and midpoint of the coefficients from Park et al. 2018[31]. This was the largest study, included UK patients, and reports the coefficients to

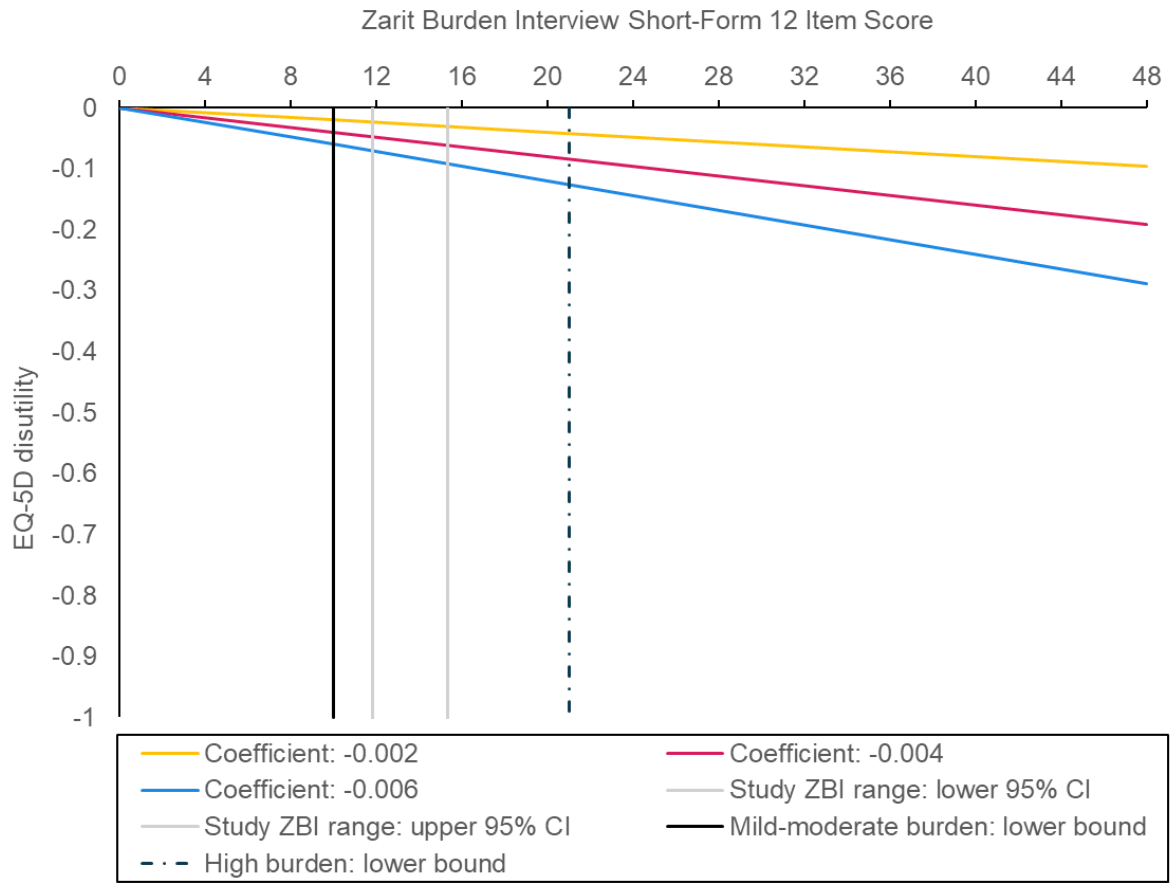
three decimal places rather than two, thus avoiding inaccuracies due to rounding. The same data is presented in Figure 2, with grey lines showing the range of ZBI scores within the source study.

Table 9: EQ-5D disutilities by ZBI-12 item categories

ZBI caregiving burden categories	ZBI		EQ-5D disutility with ZBI-12 EQ-5D coefficient:					
			-0.002		-0.004		-0.006	
	lower bound	upper bound	lower bound	upper bound	lower bound	upper bound	lower bound	upper bound
None - mild	0	10	0.000	-0.020	0.000	-0.040	0.000	-0.060
Mild-moderate	11	20	-0.020	-0.040	-0.040	-0.080	-0.060	-0.120
High	21	48	-0.042	-0.096	-0.084	-0.192	-0.126	-0.288

ZBI - Zarit Burden Interview

Figure 2: ZBI-12 item EQ-5D disutilities



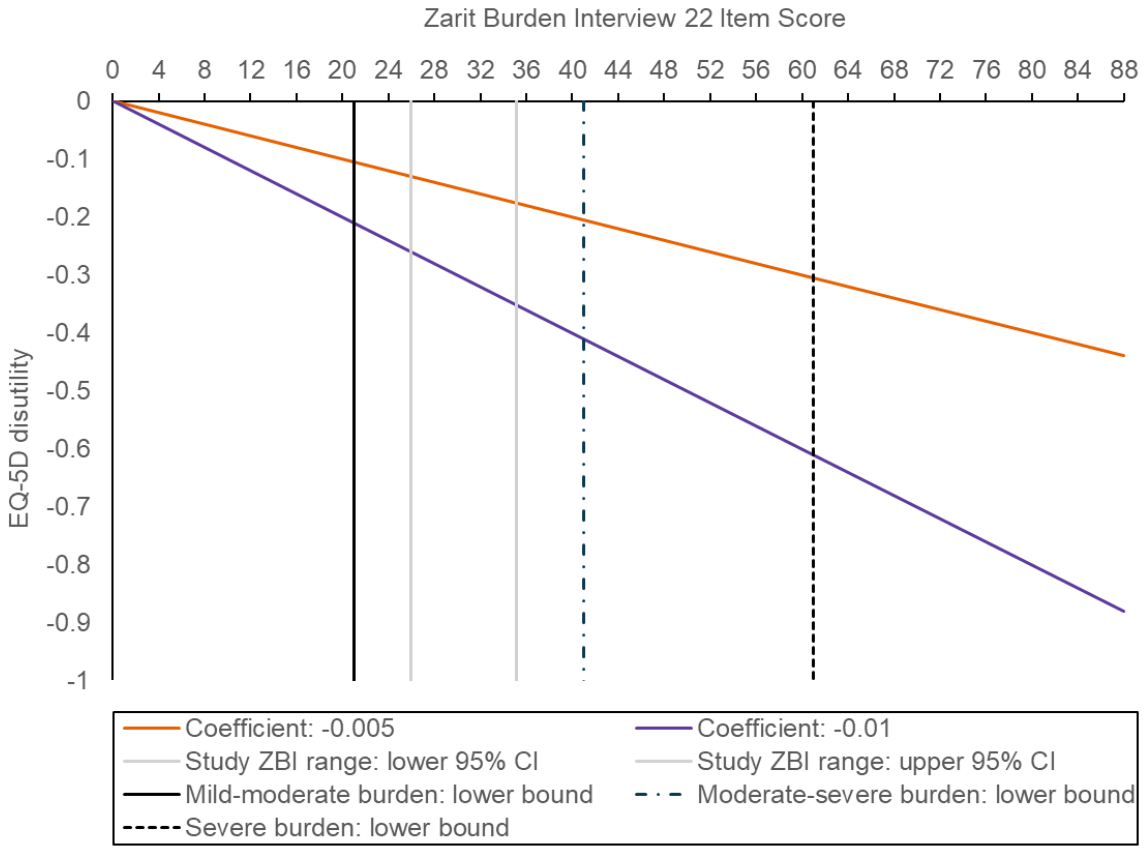
In Table 10, we have used the coefficients of -0.01 as reported by both Lee *et al*[28] and Farina *et al*,[12] and a slightly lower coefficient of -0.005 to reflect the potential lower estimate due to rounding. The same data is presented in Figure 3Figure 2, with grey lines showing the range of ZBI scores within the source study.

Table 10: EQ-5D disutilities by ZBI-22 item categories

ZBI caregiving burden categories	ZBI		EQ-5D disutility with ZBI-22 EQ-5D coefficient:			
			-0.005		-0.01	
	lower bound	upper bound	lower bound	upper bound	lower bound	upper bound
None-mild	0	20	0.000	-0.100	0.000	-0.200
Mild-moderate	21	40	-0.105	-0.200	-0.210	-0.400
Moderate-severe	41	60	-0.205	-0.300	-0.410	-0.600
Severe	61	88	-0.305	-0.440	-0.610	-0.880

ZBI - Zarit Burden Interview

Figure 3: ZBI-22 item EQ-5D disutilities



We note that these estimated carer disutilities are somewhat higher than the MMSE-based EQ-5D disutility estimates used in the economic models. To explore this further, we extracted the baseline ZBI and EQ-5D scores for the health states reported by MMSE severity in three studies (these are not adjusted for confounders). Farina et al did not find statistically significant differences between the ZBI or EQ-5D scores across the three health states, and indeed the severe health state had numerically higher EQ-5D and lower ZBI than the moderate state.[12] Reed et al found a statistically significant difference in ZBI, with higher ZBI scores for more

severe states, and a numerical but non-significant trend for EQ-5D scores to decrease with increasing severity[5]. We note that for Farina and Reed, all ZBI scores across all states are within the "mild to moderate" range with a maximum difference of 9.5 – this may partially explain why the EQ-5D values are so close together and not significantly different. Black et al found both ZBI and EQ-5D were significantly different between health states, with ZBI scores 17.5 points higher (worse) for severe and EQ-5D scores 0.089 worse for severe.[9] In Black et al, the ZBI scores spanned across categories, with prodromal and mild within the "mild to moderate" ZBI range, and moderate and severe within the ZBI "moderate to severe" range. This may partly explain why the difference in EQ-5D scores is greater (and statistically significant in Black et al), but we note that there are also other differences between the demographics of carers across the health states (for example whether the caregiver lives with the patient, carer employment status, age, sex) that are not adjusted for in this comparison. Black et al did not estimate the relationship between EQ-5D and ZBI.

Table 11: ZBI and EQ-5D scores by severity from three studies

	Alzheimer's disease severity				Statistically significant differences?
	Prodromal	Mild	Moderate	Moderate-severe / severe	
Baseline ZBI scores					
Farina		28.6	32.0	29.5	No
Reed		24.6	29.4	34.1	Yes
Black	30.3	34.3	40.9	47.8	Yes
Baseline EQ-5D scores					
Farina		0.8	0.8	0.9	No
Reed		0.86	0.85	0.82	No
Black	0.896	0.886	0.862	0.807	Yes

ZBI - Zarit Burden Interview

4.3.4.3. Caregiver burden in the economic models

We are unclear as to how the health states in the economic models relate to caregiver burden and would welcome advice from clinical experts and patients and carers with lived experience. We understand the health states to be defined by CDR rather than MMSE, which we suggest may limit the transferability of evidence between HRQoL where studies categorise HRQoL by MMSE. It is possible that the severity levels of dementia as measured by CDR correspond more closely to the burden levels using ZBI than the severity levels measured by MMSE. In this case, that may support including caregiver disutilities that more closely align with those in

Table 9 and Table 11: ZBI and EQ-5D scores by severity from three studiesTable 11. Using the lower bound of the ZBI-12 relationship with a coefficient of 0.002, and the upper bound of the ZBI-22 relationship with a coefficient of 0.005 gives a range of disutilities of 0 to -0.1 for no-mild burden, -0.02 to -0.20 for mild to moderate burden, -0.04 to -0.30 for a moderate to severe burden, and -0.04 to -0.44 for a severe burden. We suggest that it may be possible to use these ZBI categories to derive plausible estimates of the caregiver disutilities for the health states in the economic models for lecanemab and donanemab, but that particular caution needs to be given to extrapolating the relationship between ZBI and EQ-5D outside of the ZBI range observed in the studies. We prefer to use the ZBI-12 – EQ-5D relationship since this has greater accuracy and is based on a UK study, and the potential impact of assuming a linear relationship beyond the sample range is smaller with a smaller coefficient. However, we note that this provides three categories of caregiving burden, and the economic models have four health states, so we suggest using the disutilities derived from different coefficients to address this. If we used the midpoint coefficient of -0.004 and assumed that the lower bound of the mild-moderate ZBI burden category corresponded to the MCI state, this would give a disutility of -0.040. If the upper bound of the mild-moderate/lower bound of the high ZBI burden category corresponded to the Mild AD state, this would give a disutility of -0.080, using the same -0.004 coefficient. If the upper bound of the ZBI high burden category corresponded to the Moderate AD state, this would give a disutility of -0.192, using the same -0.004 coefficient. If we then used the upper bound of the ZBI high burden category for the Severe AD state, but with the -0.006 coefficient, this suggests a disutility of -0.288. We note that the maximum disutility of -0.288 is similar to the lower bound of the disutility for severe burden using the ZBI-22 categories with a coefficient of -0.005 (-0.305). We suggest that this should be considered a plausible upper bound for the maximum disutility associated with caregiving in AD, since it relies on extrapolation outside of the sample, and corresponds to a ZBI-22 score still somewhat higher than the maximum value reported in the literature (Severe AD in the study by Black *et al*.[9]). We do not consider that the results of the ZBI-22 relationship with the 0.01 coefficient are sufficiently robust to be applied in the economic model because they represent an upper bound due to rounding and assume a linear relationship that may not hold at extreme values (in reality it may flatten off).

However, the relationship between dementia severity and carers' EQ-5D via the caregiving burden is confounded by the level of formal care provided: both institutionalisation and social care provided at home. The evidence from the systematic literature review indicated that there are no sustained differences in carers' HRQoL when patients transition into institutional care.[7, 8, 41] The evidence for the interaction between social care received at home, and carer's HRQoL is less clear, since none of the studies reported, analysed or adjusted for the receipt of formal

care. There is possibly an interaction between unpaid care, formal care, and the type of care provided by informal carers and how this affects carers' HRQoL. Reed et al found that the change in carer's EQ-5D was not statistically significantly correlated with change in T-IADL which measures the time spent on instrumental activities of daily living (cooking, cleaning, taking medication, laundry, shopping, finances, communication and transport) rather than personal care activities (bathing, dressing, toileting, moving around, transferring, and eating). It is possible that the caring tasks provided by unpaid and formal carers differ, and that these different tasks have a differential effect on carers' HRQoL.

We note that the study which we believe informs the costs of social care in the model[49] uses MMSE to define severity, and the costs of both social care and unpaid care increase as severity increases.

4.3.4.4. Number of carers

We note that in the lecanemab and donanemab appraisals, the committees preferred to apply the disutilities from Reed et al.[5] to 1.8 carers, since the GERAS study on which Reed was based reported people with Alzheimer's disease had an average of 1.8 carers. We were unable to locate the source of the 1.8 figure but agree it would be appropriate in principle to include additional caregiver's HRQoL, where supported by evidence for the number of carers and relative HRQoL effect sizes. We believe it is feasible that part of the reason that the EQ-5D disutilities from GERAS are lower than might be expected is because there were additional caregivers also experiencing an HRQoL impact.

However, we do not believe that HRQoL estimates from the vignette studies should be applied to multiple carers. The descriptions of the health states in the vignette studies refer to "having responsibility" for the patient and their care and make no reference to other additional unpaid carers. We believe that if the vignettes are considered the most appropriate source of carers' HRQoL, the values from these should be applied to 1 carer.

Our ZBI-EQ-5D mapped disutilities assume that the health states in the model, which range from CDR-SB 0.5 to 3, correspond to ZBI levels ranging from no-mild burden to severe burden. We have been unable to identify definitive evidence to support this assumption and would welcome clinical and patient/carer expertise as to whether this is true. We recognise that the committee may wish to use these disutilities to support their choice of utility source (vignettes or GERAS[5]) rather than using them as an additional alternative source of data. However, we would suggest that the size of our ZBI-EQ-5D mapped disutilities should be

applied to 1 caregiver, since it seems unrealistic that multiple carers could both experience the high/severe burden – it seems more plausible that the entire ZBI score ranges represent the total caregiving burden across carers, which may be split across multiple people with a proportionate reduction for each. Furthermore, our estimates are based on out-of-sample extrapolation and the relationship between ZBI and EQ-5D is unlikely to be linear, so our estimates may be unreliable at very high or low values.

5. CONCLUSION & RECOMMENDATIONS

We identified 46 studies of caregivers of people with mild cognitive impairment or dementia due to Alzheimer's disease that used EQ-5D to measures HRQoL, demonstrating how widely EQ-5D is in this population. Many of the studies analysed the relationship between EQ-5D and one other variable, which in some cases is described as testing "convergent validity", but we note that these unadjusted comparisons are subject to potential confounding which makes it difficult to isolate the effect of one individual variable (such as caregiving) on EQ-5D.

In analyses which adjusted for (some) potential confounders, we found that there is evidence that EQ-5D responds to important factors in caring for people with Alzheimer's disease, most notably caregiving burden as measured by ZBI. We recognise that the correlation between change in EQ-5D and change in ZBI in the GERAS study by Reed *et al.*[5] was weak, but other factors will also affect carers' EQ-5D, and evidence from other studies provided statistically significant effects (at some time points) and consistent, non-negligible effect sizes. We propose that this relationship is useful in understanding the potential EQ-5D disutilities associated with differing levels of caregiving burden in Alzheimer's disease.

Studies reporting the relationship between carer's EQ-5D and Alzheimer's disease severity as measured by MMSE tended to find small and often report non-significant effects. We question whether categorisation by MMSE captures the full burden of caregiving in this population and note that ZBI scores tended to be within a fairly small range across MMSE states.

We did not find any evidence to support lower caregiver utilities when patients move into institutionalised care. The interaction and potential substitution effects between formal at-home care and informal care are important considerations in interpreting evidence in this population. Formal care was not well reported or adjusted for in studies, which likely confounds some of the estimates. Similarly, the definition of caregivers varied, and the

involvement of additional caregivers was often not measured or accounted for, which causes complexity when estimating the total caregiving HRQoL effects.

We have concerns that focussing effects in the vignettes led to them over-estimating the disutility associated with caregiving for people with Alzheimer's disease, but otherwise consider that the vignettes were well conducted. However, we note that NICE's hierarchy of evidence for HRQoL places EQ-5D at the top, with further steps (other generic measures, and condition-specific measures) between EQ-5D and vignettes – these steps have not been explored.

We believe that our systematic review has confirmed that EQ-5D is appropriate in this population and has provided an alternative source of EQ-5D disutilities based on the ZBI-EQ-5D mapping. However, there is still a need for a UK-specific study of the HRQoL of caregivers of people with Alzheimer's disease, that includes EQ-5D (and potentially other HRQoL measures) and measures and adjusts for the effects of confounders including the amount and type of formal care (and how this is funded), and unpaid care provided by multiple people. This study would be invaluable in informing future appraisals in Alzheimer's disease, and more broadly in identifying populations in which caregivers' HRQoL is particularly affected, and the extent to which additional formal care can address this. There is also scope for further research and guidance to define exactly how to demonstrate whether EQ-5D is appropriate or not, particularly given the problems of confounding in tests of univariate analysis as a claim of convergent validity.

6. DISCUSSION & LIMITATIONS

Our review systematically identified evidence on which aspects of patient health and caregiving significantly affect carers' HRQoL. We searched multiple databases and sourced evidence from two company submission as well as the wider literature. We cannot be certain that we did not miss any potentially relevant studies: we did not search grey literature, our searches were specific (for example we did not search for broader terms relating to quality of life), and one reviewer screened the studies. However, we are reassured that we identified all of the studies that were included in the systematic review by Faller *et al.*[24] (plus more), and that we came to the same general conclusion that EQ-5D is appropriate for measuring carers' HRQoL. While we cannot rule out that we have missed potentially relevant studies, we consider it highly unlikely that these studies would have changed our conclusions.

The studies we identified are, as discussed, subject to unknown confounding due to unreported levels of care provision – either through additional informal carers, formal adult social care, or long-term care in a nursing home. This may be a particular concern with studies where the provision of formal care, and/or cultural expectations around informal caregiving, differ from the UK context. For this reason, it may be more appropriate to consider the relationship between the burden of caregiving and EQ-5D, rather than between AD patient health states and EQ-5D.

We have used evidence from the literature to estimate EQ-5D carer disutilities for caregiving burden reported on the ZBI scale. While we believe this is useful for informing the potential size of carer disutilities in AD, it assumes that the linear relationship between carers' EQ-5D and ZBI can be extrapolated outside the sample used to develop the relationship. We consider that this is uncertain, particularly at a high level of caregiving burden.

Overall, we consider that our review adds to the body of evidence demonstrating that unpaid caregiving in AD has a detrimental effect on carers' HRQoL. While it has its limitations, our research provides insight for the effect of AD caring on EQ-5D and provides additional data for populating economic models.

7. REFERENCES

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8. APPENDIX

8.1. Search Strategy

8.1.1. EQ-5D specific searches

8.1.1.1. Search summary

Database	Platform	Search date	No. of results
MEDLINE All	Ovid	17/04/2026	188
Embase	Ovid	17/04/2026	430
EconLit	Ovid	17/04/2026	2
PsycInfo	Ovid	17/04/2026	90
Total results before deduplication			**710**

No date or publication language limits were applied. In Embase, pre-prints (n = 0) and ClinicalTrials.gov records (n=38) were excluded.

8.1.1.2. Search strategies

Ovid MEDLINE(R) ALL <1946 to April 16, 2026>

1 Caregivers/ 61805
2 (carer* or caregiver*).ti,ab,kf. 141971
3 ("loved one*" or parent* or mother* or father* or grandparent* or grandmother* or grandfather* or sibling* or brother* or sister* or child or children or daughter* or son* or spouse* or wife or wives or husband* or partner*).ti,ab. 2671651
4 1 or 2 or 3 2761909
5 (eq or euroqol or euro qol or eq5d or eq 5d or euroqual or euro qual).ti,ab,kf. 29862
6 (EQ-5D or EQ-5D-5L or EQ-5D-3L).ti,ab,kf. 16996
7 5 or 6 29862
8 Alzheimer Disease/ 140879
9 exp Dementia/ 238469
10 (dementia* or alzheimer*).ti,ab. 332626
11 ((mild* or early* or preclinical or pre-clinical) adj2 (cognitive impair* or cognitive dysfunction or cognitive decline)).ti,ab. 34035
12 8 or 9 or 10 or 11 385883
13 4 and 7 and 12 188

Embase <1974 to 2026 Week 15>

1 exp caregiver/ 165436
2 (carer* or caregiver*).ti,ab,kf. 209277

3 ("loved one*" or parent* or mother* or father* or grandparent* or grandmother* or grandfather* or sibling* or brother* or sister* or child or children or daughter* or son* or spouse* or wife or wives or husband* or partner*).ti,ab. 3568216
4 1 or 2 or 3 3711006
5 exp "european quality of life 5 dimensions questionnaire"/ 29923
6 (eq or euroqol or euro qol or eq5d or eq 5d or euroqual or euro qual).ti,ab,kf. 52023
7 (EQ-5D or EQ-5D-5L or EQ-5D-3L).ti,ab,kf. 32481
8 5 or 6 or 7 58705
9 exp Alzheimer disease/ 322120
10 exp dementia/ 566354
11 (dementia* or alzheimer*).ti,ab. 476576
12 ((mild* or early* or preclinical or pre-clinical) adj2 (cognitive impair* or cognitive dysfunction or cognitive decline)).ti,ab. 55741
13 9 or 10 or 11 or 12 653975
14 4 and 8 and 13 468
15 limit 14 to "clinical trials (clinicaltrials.gov)" 38
16 limit 14 to "preprints (unpublished, non-peer reviewed)" 0
17 15 or 16 38
18 14 not 17 430

Econlit <1886 to April 09, 2026>

1 (carer* or caregiver*).ti,ab. 1104
2 ("loved one*" or parent* or mother* or father* or grandparent* or grandmother* or grandfather* or sibling* or brother* or sister* or child or children or daughter* or son* or spouse* or wife or wives or husband* or partner*).ti,ab. 77586
3 1 or 2 78146
4 (eq or euroqol or euro qol or eq5d or eq 5d or euroqual or euro qual).ti,ab. 496
5 (EQ-5D or EQ-5D-5L or EQ-5D-3L).ti,ab. 304
6 4 or 5 496
7 (dementia* or alzheimer*).ti,ab. 320
8 ((mild* or early* or preclinical or pre-clinical) adj2 (cognitive impair* or cognitive dysfunction or cognitive decline)).ti,ab. 10
9 7 or 8 322
10 3 and 6 and 9 2

APA PsycInfo <1806 to April 2026 Week 2>

1 caregivers/ 44595
2 (carer* or caregiver*).ti,ab. 84627
3 ("loved one*" or parent* or mother* or father* or grandparent* or grandmother* or grandfather* or sibling* or brother* or sister* or child or children or daughter* or son* or spouse* or wife or wives or husband* or partner*).ti,ab. 1109226
4 1 or 2 or 3 1154128
5 (eq or euroqol or euro qol or eq5d or eq 5d or euroqual or euro qual).ti,ab. 4903
6 (EQ-5D or EQ-5D-5L or EQ-5D-3L).ti,ab. 3071
7 5 or 6 4903
8 alzheimer's disease/ 64885

9 exp dementia/ 105091
10 (dementia* or alzheimer*).ti,ab. 132541
11 ((mild* or early* or preclinical or pre-clinical) adj2 (cognitive impair* or cognitive dysfunction or cognitive decline)).ti,ab. 17464
12 8 or 9 or 10 or 11 139837
13 4 and 7 and 12 90

8.2. *Broader* HRQoL searches

8.2.1. Search summary

Database	Platform	Search date	No. of results
MEDLINE All	Ovid	17/04/2026	123
Embase	Ovid	17/04/2026	270
EconLit	Ovid	17/04/2026	0
PsycInfo	Ovid	17/04/2026	45
Total results before deduplication			**438**

A date limit of 2022 – current was applied to these searches to capture literature published since the literature searches conducted by the companies. In Embase, pre-prints (n = 0) and ClinicalTrials.gov records (n=33) were excluded.

8.2.1.1. Search strategies

Ovid MEDLINE(R) ALL <1946 to April 16, 2026>

1 Caregivers/ 61805
2 (carer* or caregiver*).ti,ab,kf. 141971
3 ("loved one*" or parent* or mother* or father* or grandparent* or grandmother* or grandfather* or sibling* or brother* or sister* or child or children or daughter* or son* or spouse* or wife or wives or husband* or partner*).ti,ab. 2671651
4 1 or 2 or 3 2761909
5 (eq or euroqol or euro qol or eq5d or eq 5d or euroqual or euro qual).ti,ab,kf. 29862
6 (EQ-5D or EQ-5D-5L or EQ-5D-3L).ti,ab,kf. 16996
7 ("health related quality of life" or "health-related quality of life" or HRQoL).ti,ab. 72668
8 5 or 6 or 7 94246
9 Alzheimer Disease/ 140879
10 exp Dementia/ 238469
11 (dementia* or alzheimer*).ti,ab. 332626
12 ((mild* or early* or preclinical or pre-clinical) adj2 (cognitive impair* or cognitive dysfunction or cognitive decline)).ti,ab. 34035
13 9 or 10 or 11 or 12 385883
14 4 and 8 and 13 453
15 limit 14 to yr="2022 -Current" 123

Embase <1974 to 2026 Week 15>

1 exp caregiver/ 165436
2 (carer* or caregiver*).ti,ab,kf. 209277
3 ("loved one*" or parent* or mother* or father* or grandparent* or grandmother* or grandfather* or sibling* or brother* or sister* or child or children or daughter* or son* or spouse* or wife or wives or husband* or partner*).ti,ab. 3568216
4 1 or 2 or 3 3711006
5 exp "european quality of life 5 dimensions questionnaire"/ 29923
6 (eq or euroqol or euro qol or eq5d or eq 5d or euroqual or euro qual).ti,ab,kf. 52023
7 (EQ-5D or EQ-5D-5L or EQ-5D-3L).ti,ab,kf. 32481
8 ("health related quality of life" or "health-related quality of life" or HRQoL).ti,ab. 113130
9 5 or 6 or 7 or 8 156901
10 Alzheimer Disease/ 322097
11 exp Dementia/ 566354
12 (dementia* or alzheimer*).ti,ab. 476576
13 ((mild* or early* or preclinical or pre-clinical) adj2 (cognitive impair* or cognitive dysfunction or cognitive decline)).ti,ab. 55741
14 10 or 11 or 12 or 13 653975
15 4 and 9 and 14 926
16 limit 15 to yr="2022 -Current" 303
17 limit 16 to "clinical trials (clinicaltrials.gov)" 33
18 limit 17 to "preprints (unpublished, non-peer reviewed)" 0
19 17 or 18 33
20 16 not 19 270

Econlit <1886 to April 09, 2026>

1 (carer* or caregiver*).ti,ab. 1104
2 ("loved one*" or parent* or mother* or father* or grandparent* or grandmother* or grandfather* or sibling* or brother* or sister* or child or children or daughter* or son* or spouse* or wife or wives or husband* or partner*).ti,ab. 77586
3 1 or 2 78146
4 (eq or euroqol or euro qol or eq5d or eq 5d or euroqual or euro qual).ti,ab. 496
5 (EQ-5D or EQ-5D-5L or EQ-5D-3L).ti,ab. 304
6 ("health related quality of life" or "health-related quality of life" or HRQoL).ti,ab. 299
7 4 or 5 or 6 703
8 (dementia* or alzheimer*).ti,ab. 320
9 ((mild* or early* or preclinical or pre-clinical) adj2 (cognitive impair* or cognitive dysfunction or cognitive decline)).ti,ab. 10
10 8 or 9 322
11 3 and 7 and 10 3
12 limit 11 to yr="2022 -Current" 0

APA PsycInfo <1806 to April 2026 Week 2>

1 caregivers/ 44595
2 (carer* or caregiver*).ti,ab. 84627
3 ("loved one*" or parent* or mother* or father* or grandparent* or grandmother* or grandfather* or sibling* or brother* or sister* or child or children or daughter* or son* or spouse* or wife or wives or husband* or partner*).ti,ab. 1109226
4 1 or 2 or 3 1154128
5 (eq or euroqol or euro qol or eq5d or eq 5d or euroqual or euro qual).ti,ab. 4903
6 (EQ-5D or EQ-5D-5L or EQ-5D-3L).ti,ab. 3071
7 ("health related quality of life" or "health-related quality of life" or HRQoL).ti,ab. 15834
8 5 or 6 or 7 19085
9 alzheimer's disease/ 64885
10 exp dementia/ 105091
11 (dementia* or alzheimer*).ti,ab. 132541
12 ((mild* or early* or preclinical or pre-clinical) adj2 (cognitive impair* or cognitive dysfunction or cognitive decline)).ti,ab. 17464
13 9 or 10 or 11 or 12 139837
14 4 and 8 and 13 232
15 limit 14 to yr="2022 -Current" 45

8.2.1.2. Deduplication

Results from both sets of searches were combined and deduplicated in EndNote before screening. Before deduplication, there were 1,148 results, with 558 remaining after deduplication.

8.3. Studies reporting univariate analysis

Table 12: Summary of studies reporting unadjusted comparisons/univariate analysis

Study	HRQoL measure 3L or 5L + value set?	Caregivers' characteristics				Care setting	Definition of caregiver	Patient severity inclusion criteria	Study design	Analysis	Country
		Sample size	Number (%) of females	Mean age (SD)	Caregiver's relationship to patient (%)						
Sokolova 2024[23]	EQ-5D-5L, value set NR	212	130 (61.3%)	47.4 (17.0)	Spouse: 21.7%	NR	NR	Mild or early, moderate or middle stage and severe or late-stage dementia based on MMSE	Cross-sectional	non-parametric Wilcoxon-rank test, the Kruskal-Wallis equality-of-populations rank test	Australia
Choi 2024[50]	EQ-5D-5L, country-specific value set (Korea)	47	32 (68.1%)	67.02 (11.49)	Spouse: 59.6%	Living with patients: 85.1%	Residing and caring for PwD or providing care more than twice a week when not living together	NR	Cross-sectional	Spearman's rank correlation, Pearson's correlation	Korea

Study	HRQoL measure 3L or 5L + value set?	Caregivers' characteristics				Care setting	Definition of caregiver	Patient severity inclusion criteria	Study design	Analysis	Country
		Sample size	Number (%) of females	Mean age (SD)	Caregiver's relationship to patient (%)						
Reed 2017[5]	EQ-5D-3L (country-specific value set+)	1495	958 (64.2%)	67.3 (12.0)	Spouse: 65.9%	Living with patient (community dwelling): 76%	Primary caregiver, responsible for the patient for at least 6 months per year	Mild, moderate and severe AD based on MMSE scores	Observational study	Spearman's rank correlation	France, Germany and UK
Lin 2025[51]	EQ-5D-5L, country-specific value set (US)	176	111 (63.0%)	≤ 60 yr: 43.2%, 61-70 yr: 22.7%, 71-80 yr:21.6%, ≥ 80 yr: 12.5%	Spouse: 47.6%	Nursing home:23.9 %	who self-identified as a current caregiver of someone with MCI or AD	NR	Cross-sectional	One-way analysis of variance (ANOVA)	US
Mesterton 2010 [16]	EQ-5D, value set NR	Unclear	NR	NR	NR	living with patients:61 % mild: 87% , moderate: 54% , severe: 29%	NR	Mild, moderate and severe AD based on MMSE	Cross-sectional	One-way analysis of variance (ANOVA), Chi-square test	Sweden
Wammes 2024[52]	EQ-5D, country-specific	237	158 (66.79 %)	65.98 (11.93)	Spouse: 59.83%	Community dwelling	Primary informal caregiver	MMSE	Prospective, observational , cohort study	Bivariate analysis	Netherlands

Study	HRQoL measure 3L or 5L + value set?	Caregivers' characteristics				Care setting	Definition of caregiver	Patient severity inclusion criteria	Study design	Analysis	Country
		Sample size	Number (%) of females	Mean age (SD)	Caregiver's relationship to patient (%)						
	value set (Dutch)						responsible for caring for PwD				
Stephan 2013[53]	EQ-5D, value set NR	234	163 (69.7%)	61.1 (11.8)	Spouse: 26.5%	Living together with caregiver: 28.2%	Being the person most involved in caregiving and visiting the PwD at least twice a month	dementia formally diagnosed by a physician (and Mini-Mental State Examination (MMSE ≤24),	Prospective cohort study	Spearman's rank correlation	Germany
Potter 2023[54]	EQ-5D-5L, value set NR	107	67 (63%)	67 (range: 41-90)	Spouse: 81%	Living with patients: 68%	regular support from an informal carer were confirmed by clinical staff	MCI or dementia, severity staging NR	Cross-sectional survey	Spearman's rank correlation	UK
Pothiban 2020[55]	EQ-5D-3L, value set NR	76	77.63%	52.13 (10.23)	Spouse: 75%	Community dwelling	Have experience in taking care of older	Patients with MMSE (0-21)	Cross-sectional	Spearman's rank correlation	Thailand

Study	HRQoL measure 3L or 5L + value set?	Caregivers' characteristics				Care setting	Definition of caregiver	Patient severity inclusion criteria	Study design	Analysis	Country
		Sample size	Number (%) of females	Mean age (SD)	Caregiver's relationship to patient (%)						
							people with dementia for at least 3 months	Mean: 13.50 (SD:4.81)			
Perry Duxbury 2020[56]	EQ-5D-5L, country-specific value set (UK)	451	66.4%	66.4	Spouse: 63.9%	Home dwelling	NR	Patients with mild to moderate dementia based on CDR	Cross-sectional	Spearman's rank correlation	Germany, Ireland, Italy, the Netherlands,Norway, Portugal, Sweden and the UK
Oremus 2014[42]	EQ-5D, country-specific value set (Canada)	216	143 (66%)	Median: 69 (range: 59-77)	Spouse: 68%	Living with patient: 75%	Primary informal carer	Mild and moderate AD based on FAST	Cross-sectional	Subgroup stratification by disease severity	Canada
Pedersen 2026[57]	EQ-5D-5L, value set NR	375	280 (75%)	68.2 (11.2)	Spouse: 70%	Community dwelling: 86% Residential care: 14%	Adult family caregivers	NR	Cross-sectional	Spearman's rank correlation	Denmark

Study	HRQoL measure 3L or 5L + value set?	Caregivers' characteristics				Care setting	Definition of caregiver	Patient severity inclusion criteria	Study design	Analysis	Country
		Sample size	Number (%) of females	Mean age (SD)	Caregiver's relationship to patient (%)						
McLoughlin 2020[27]	EQ-5D-5L, value set NR	576	65%	62 (11)	Spouse: 35%	Living with patient: 46%	NR	NR	Longitudinal‡	Spearman's rank correlation	UK
Majoni 2017[34]	EQ-5D-3L, country-specific value set (Canada?)	200 Retired: 140 Employed: 60	Retired: 62% Employed: 72%	Retired: 74 (68-80) Employed:56 (51-62)	Spouse, Retired: 86% Spouse, Employed: 30%	Living with patients Retired: 88% Employed: 47%	Primary informal caregiver	NR	Cross-sectional	Chi-square or Fisher exact test	Canada
Madruga 2020[58]	EQ-5D-3L, value set NR	54	100%	60.6 (6.6)	Spouse: 79.6%	Living with patients: 74.1%	Female unpaid family caregiver, aged ≥ 50 yr, providing at least 20 hr of in-person care per week	NR	Cross-sectional	Pearson's rank correlations with the Bonferroni adjustment	Spain
Lee 2025[28]	EQ-5D-5L, value set NR	130	92 (70.8)	66.83 (13.4)	Spouse: 54.6%	Community	NR	Level 4 (mild dementia) and level 5 or above	Cross-sectional	Pearson's rank correlations	Australia

Study	HRQoL measure 3L or 5L + value set?	Caregivers' characteristics				Care setting	Definition of caregiver	Patient severity inclusion criteria	Study design	Analysis	Country
		Sample size	Number (%) of females	Mean age (SD)	Caregiver's relationship to patient (%)						
								(moderate to severe dementia) based on the GDRS.			
Im 2022[59]	EQ-5D-5L, country-specific value (US)	172 Whites: 36, Africans Americans: 41, Hispanics: 40, Asians: 50	100%	Whites: 44.86 (3.90), Africans Americans: 46.90 (5.53), Hispanics: 47.04 (5.29), Asians: 51.54 (5.29)	Whites: 97.1%, Africans Americans:95%, Hispanics:97.5%, Asians: 100%	Community dwelling	family caregivers providing unpaid assistance (at least average 4 hours per day) for a person in an early to middle stage of AD (Clinical Dementia Rating of ≥ 1) and had no plan for institutionalization in the following six months.	early to middle stage of AD (Clinical Dementia Rating of ≥ 1)	Cross-sectional	Hierarchical multiple linear regression	US

Study	HRQoL measure 3L or 5L + value set?	Caregivers' characteristics				Care setting	Definition of caregiver	Patient severity inclusion criteria	Study design	Analysis	Country
		Sample size	Number (%) of females	Mean age (SD)	Caregiver's relationship to patient (%)						
Igarashi 2020[60]	EQ-5D-5L, country-specific value set (Japan)	635 (with 50.6% being primary caregivers)	312 (49.1%)	51.2 (11.3)	NR	Living at home: 77.3%	*Primary caregiver*: families living with dementia who were mainly taking care of persons with dementia, *Non-primary caregiver*: families living with dementia providing secondary care or family members without caregiving activities.	NR	Cross-sectional	Bivariate analysis	Japan
Hendriks 2017[61]	EQ-5D-3L,	173	114 (68.7%)	62.0 (13.7)	Spouse: 44.2%	Living with patients: 52.7%	Informal carer	MMSE	Cross-sectional	Pearson's rank correlations	UK

Study	HRQoL measure 3L or 5L + value set?	Caregivers' characteristics				Care setting	Definition of caregiver	Patient severity inclusion criteria	Study design	Analysis	Country
		Sample size	Number (%) of females	Mean age (SD)	Caregiver's relationship to patient (%)						
	used the UK time trade-off-based index values										
Haikio 2020[35]	EQ-5D-5L, value set NR	188	134 (71%)	60 yr (25 to 84)	NR	Living in urban area: 87%	A family member, neighbour or friend who, carries out tasks of a supportive nature that go beyond normal relationships of reciprocity among adults[†]	Mild and severe dementia based on Norwegian translation of the Berger Dementia Scale (BDS)	Cross-sectional	Both bivariate and multivariate regression	Norway
Ferrero-Sereno 2024[62]	EQ-5D-3L, value set NR	59	NR	59.30 (10.58)	Spouse: 35.6%	NR	Informal caregiver performing caregiving tasks for >20 hr a week	NR	Cross-sectional	Step-wise regression	Spain

Study	HRQoL measure 3L or 5L + value set?	Caregivers' characteristics				Care setting	Definition of caregiver	Patient severity inclusion criteria	Study design	Analysis	Country
		Sample size	Number (%) of females	Mean age (SD)	Caregiver's relationship to patient (%)						
							and at least 3 months and having the willingness to continue caring for their relative for one year.				
Dixon 2006[36]	EQ-5D-3L, value set NR	64	59%	63 (SD NR)	Spouse: 52%	NR	NR	Dementia diagnosis was categorised using three-digit ICD codes (10th revision). Severity of dementia was not reported.	Cross-sectional	Multivariate regression	UK

Study	HRQoL measure 3L or 5L + value set?	Caregivers' characteristics				Care setting	Definition of caregiver	Patient severity inclusion criteria	Study design	Analysis	Country
		Sample size	Number (%) of females	Mean age (SD)	Caregiver's relationship to patient (%)						
Alvira 2017[63]	EQ-5D, value set NR	287	206 (71.8%)	64.7 (12.7)	Spouse: 38.7%	LTCI: 113 (39.37%) HC: 174 (60.63%)	NR	MMSE	Cross-sectional	Spearman's rank correlation	Spain
Mancini 2025[64]	EQ-5D-3L, value set NR	34	29 (85%)	56.0 (IQR: 49.0, 75.0)	NR	NR	NR	No CI, MCI and dementia based on MMSE	Longitudinal	Mann–Whitney U test	Italy
Froehlich 2021 [17]	EQ-5D-5L, value set NR	616	374 (60.71 %)	67.68(12.94)	69.64%	Community dwelling	Primary caregivers (defined as spending at least 7 hours a week caring for the patient)	Mild and moderate AD based on physician routine clinical practice and MMSE	Longitudinal	Chi-square test	Germany, Spain and UK
Potter 2020[65]	EQ-5D-5L, value set NR	107	NR	NR	NR	NR	NR	MCI or dementia, unspecified severity staging	Cross-sectional	One-way ANOVA	England
Darba 2010[66]	EQ-5D, value set NR	394	NR	NR	NR	NR	NR	MCI to severe dementia	Cross-sectional	Person's rank correlation	NR

Study	HRQoL measure 3L or 5L + value set?	Caregivers' characteristics				Care setting	Definition of caregiver	Patient severity inclusion criteria	Study design	Analysis	Country
		Sample size	Number (%) of females	Mean age (SD)	Caregiver's relationship to patient (%)						
								based on MMSE			
Noto 2024[67]	EQ-5D-5L, value set NR	705	NR	NR	NR	NR	NR	NR	Cross-sectional	Correlation analysis	Japan
Pittalis 2017[68]	EQ-5D-3L, value set NR	56	79%	56 (SD: NR)	Children: 57%	Community ?	NR	NR	Cross-sectional	Non-parametric tests	Ireland?
Handels 2018[10]	EQ-5D-5L, country-specific value set +	451	67%	66 (13)	Spouse/partner: 64%	Community dwelling Living together with patients: 72%	NR	Mild or moderate dementia based on MMSE	Cross-sectional	ANOVA, Chi-square tests	Germany, Ireland, Italy, the Netherlands, Norway, Portugal, Swede and UK
Van-Hezik Wester 2023[14]	EQ-5D-5L, country-specific value set (Dutch)	68	51 (50%)	49 (17)	Partner: 20%	Community dwelling: 36 (52.94%) Institutionalised: 32 (47.05%)	NR	Mild, moderate and severe AD validated by experienc	Cross-sectional	ANOVA, Kruskal-Wallis rank test, Fisher exact test	Netherlands

Study	HRQoL measure 3L or 5L + value set?	Caregivers' characteristics				Care setting	Definition of caregiver	Patient severity inclusion criteria	Study design	Analysis	Country
		Sample size	Number (%) of females	Mean age (SD)	Caregiver's relationship to patient (%)						
								e clinicians.			
Lopez-Bastida 2006[15]	EQ-5D, social tariff	237	179 (75.5%)	55.2 (14.5)	Spouse: 38.4%	Community dwelling	Primary family caregiver: the family member who provided the most day-to-day hands-on care for patient with AD	Mild, moderate and severe AD measured by CDR	Cross-sectional	NR	Spain

AD - Alzheimer's disease; ANCOVA - Analysis of Covariance; BDS - Berger Dementia Scale; CDR – Clinical Dementia Rating; CI - cognitive impairment; EQ-5D-3L – EQ5D- 3- levels; EQ-5D-5L – EQ5D- 5- levels; FAST - functional assessment staging in AD; GDRS - Global Deterioration Scale; HC - home care; HRQOL - health-related quality of life; ICD - International Classification of Diseases; ILTC - institutional long-term care; LTCI - long-term care institution; MCI - mild cognitive impairment; MMSE - Mini-Mental State Examination; NR - not reported; PwD - people with dementia; SD - standard deviation, yr - years

Table 13: Statistically significant associations between carers' EQ-5D and other variables in univariate analyses

Study	Weekly caregiving hours	Caregiving situation / factors	Patient severity	Other HRQoL measures (Carer)	ZBI	Patient HRQoL	Met needs	Caregiver reaction Assessment	Setting / living arrangement
Sokolova 2024[23]	Y	emotionally and physically exhausted: Y relationship problems: Y difficulties getting social support: Y unable to do things they enjoy: Y .	MMSE: Mild vs mod/severe: Y Mod vs severe: N						
Choi 2024[50]				HINT-8: Y	Y				
Reed 2017[5]		T-IADL: baseline: Y 18 month: Y	MMSE: Y		baseline: Y 18 month: Y				
Lin 2025[51]			Identified set of symptoms: N						
Mesterton 2010[16]			MMSE: N						
Wammes 2024[52]						Y (EQ-5D)	PwD: N Proxy: Y		
Stephan 2013[53]								Impact on health: Y	

Study	Weekly caregiving hours	Caregiving situation / factors	Patient severity	Other HRQoL measures (Carer)	ZBI	Patient HRQoL	Met needs	Caregiver reaction Assessment	Setting / living arrangement
Potter 2023[54]				LTCQ-Carer: Y					
Pothiban 2020[55]		Positive aspects: N Close relationships: Y Stress: Y Self-efficacy: N Perceived support: Y Burden: Y							
Perry Duxbury 2020[56]				ICECAP-O: Y (weak)					
Oremus 2014[42]			FAST: N						
Pedersen 2026[57]				CES: Y (weak)					

Study	Weekly caregiving hours	Caregiving situation / factors	Patient severity	Other HRQoL measures (Carer)	ZBI	Patient HRQoL	Met needs	Caregiver reaction Assessment	Setting / living arrangement
McLoughlin 2020[27]		Duration of caring: Y Hours per week: Y Personal care: Y Main carer: Y Involvement of others: N		CES: Y (weak) CarerQoL-7D: Y (moderate) ASCOT-Carer: Y (moderate) ICECAP-A: Y (moderate)		EQ-5D: Y			
Majoni 2017[34]		Duration of caring: N Caregiving perception: N	Undefined. Mild vs Moderate: N						Y
Madruga 2020[58]		Years caring: Y Overburden: Y							
Lee 2025[28]					Y				

Study	Weekly caregiving hours	Caregiving situation / factors	Patient severity	Other HRQoL measures (Carer)	ZBI	Patient HRQoL	Met needs	Caregiver reaction Assessment	Setting / living arrangement
Im 2022[59]		Reactions: Y Behavioural skills: Y Attitudes to AD: N Attitudes to caregiving: Y							
Igarashi 2020[60]		Primary vs non-primary: Y							
Hendriks 2017[61]						DemQOL-Proxy: Y			
Haikio 2020[35]		Health literacy: Y							
Ferrero-Sereno 2024[62]		Overload: Y							
Dixon 2006[36]						EQ-5D: N			

Study	Weekly caregiving hours	Caregiving situation / factors	Patient severity	Other HRQoL measures (Carer)	ZBI	Patient HRQoL	Met needs	Caregiver reaction Assessment	Setting / living arrangement
Alvira 2017[63]								Impact on health: Y Impact on finances: Y Impact on schedule: Y Self-esteem: N Family support: N	
Mancini 2025[64]			MMSSE MCI vs dementia: N						
Froehlich 2021[17]			MMSE: Moderate vs mild: N						
Potter 2020[65]		Carer's number of comorbid conditions: Y							
Lin 2025[51]			MMSE: MCI, mild, moderate, severe: N						Nursing home vs community: NR

Study	Weekly caregiving hours	Caregiving situation / factors	Patient severity	Other HRQoL measures (Carer)	ZBI	Patient HRQoL	Met needs	Caregiver reaction Assessment	Setting / living arrangement
Darba 2010[66]			MMSE : N Cognitive component score: Y Functional Component score: Y Behaviour competent score: Y Dependence Scale: Y						
Noto 2024[67]				ASCOT-Carer: Y	J-ZBI-8: Y				
Pittalis 2017[68]					Y				
Handels 2018[10]							N (both patient and caregiver)		

Study	Weekly caregiving hours	Caregiving situation / factors	Patient severity	Other HRQoL measures (Carer)	ZBI	Patient HRQoL	Met needs	Caregiver reaction Assessment	Setting / living arrangement
Van-Hezik Wester 2023[14]			descriptions of 4 symptomatic stages: N						N
Lopez-Bastida 2006[15]			CDR: N						

ASCOT-Carer - adult social care outcomes toolkit for carers; CarerQoL - carer quality-of-life; CDR - Clinical Dementia Rating; CES - Carer Experience Scale; DEMQOL - Dementia quality of life; HRQoL - health-related quality of life; HINT-8 - Health-Related Quality of Life Instrument with 8 items; IQR - interquartile range; ICECAP-A - ICEpop CAPability measure for Adults; ICECAP-O - ICEpop CAPability measure for Older people; J-ZBI – Japanese Zarit Burden Interview; LTCQ-Carer - Long-term Conditions Questionnaire for Carers; PwD - people with dementia; T-IADL - time spent on instrumental activities of daily living; ZBI - Zarit Burden Interview
Y - yes; N - no; Blank - not analysed
Bold = significant at 5% level