



Spillover Effects on Caregivers' and Family Members' Utility: A Systematic Review of the Literature

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Abstract

Background A growing body of research has identified health-related quality-of-life effects for caregivers and family members of ill patients (i.e. 'spillover effects'), yet these are rarely considered in cost-effectiveness analyses (CEAs).

Objective The objective of this study was to catalog spillover-related health utilities to facilitate their consideration in CEAs.

Methods We systematically reviewed the medical and economic literatures (MEDLINE, EMBASE, and EconLit, from inception through 3 April 2018) to identify articles that reported preference-based measures of spillover effects. We used keywords for utility measures combined with caregivers, family members, and burden.

Results Of 3695 articles identified, 80 remained after screening: 8 (10%) reported spillover utility per se, as utility or disutility (i.e. utility loss); 25 (30%) reported a comparison group, either population values ($n = 9$) or matched, non-caregiver/family member or unaffected individuals' utilities ($n = 16$; 3 reported both spillover and a comparison group); and 50 (63%) reported caregiver/family member utilities only. Alzheimer's disease/dementia was the most commonly studied disease/condition, and the EQ-5D was the most commonly used measurement instrument.

Conclusions This comprehensive catalog of utilities showcases the spectrum of diseases and conditions for which caregiver and family members' spillover effects have been measured, and the variation in measurement methods used. In general, utilities indicated a loss in quality of life associated with being a caregiver or family member of an ill relative. Most studies reported caregiver/family member utility without any comparator, limiting the ability to infer spillover effects. Nevertheless, these values provide a starting point for considering spillover effects in the context of CEA, opening the door for more comprehensive analyses.

1 Background

The burden of family caregiving is familiar to most [1]. Spouses' health declines when their partners are hospitalized [2], adult children become anxious and fatigued caring for parents with dementia [3], and parents lose sleep while caring for disabled children [4]. Yet the consequences of illness in a family are in fact a complicated interplay of the physical, psychological, and emotional, ranging from strain,

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Key Points

Inclusion of caregiver and family member ('spillover') quality-adjusted life-years (QALYs) in cost-effectiveness analyses (CEAs) is recommended by multiple national guidance bodies.

Caregiver and family member QALYs can include spillover utilities (the independent utility loss due to a family member's illness) that are rarely reported in the literature; more common are caregivers'/family members' utilities, sometimes in combination with a comparator utility.

Research gaps remain in spillover effect estimation and incorporation methods, slowing the adoption of these additional measures of burden into cost-effectiveness evaluations.

grief, and guilt, to gratification, interdependence, and joy, and affect caregiving as well as non-caregiving members [5]. While some families experience solace and relief when their relative's health improves, changes in family dynamics and caregiving responsibilities may come as well: extended life for an elderly frail parent incurs extended caretaking needs; successful treatment for a severely ill child may result in a lifelong disability, with the associated care needs and emotional trauma for the parents [5–7]. The shifting locus of care to outpatient settings and the home increases families' involvement in care, and the corresponding effects on their health and well-being [1].

Current recommendations for societal perspective economic evaluation include both patients' and family members' effects in assessing the cost effectiveness of health technologies and interventions [8–11]. The effects, both health and otherwise, that are incurred by caregivers and non-caregiving family members (hereafter called 'spillover effects') are challenging, both to measure and to incorporate into cost-effectiveness analysis (CEA¹). Measures of health-related spillover effects include utility valuations, via direct or indirect utility elicitation techniques, used to calculate quality-adjusted life-years (QALYs), and valuations that adopt a broader perspective, including care-related effects, that cannot be used for QALYs but rather capture the value assigned to the caring experience [12, 13]. A recommended, QALY-based measurement approach that is suitable across the variations in effects, including patient diseases/conditions, patient/caregiver/family member relationship, and extent of caregiver/family member involvement, has yet to be identified. Moreover, incorporating spillover effects into CEA poses its own challenges; although frameworks have been proposed, questions remain and inclusion has not yet become the norm [14–16].

The costs incurred in the course of providing informal care are also recommended for inclusion in societal perspective CEAs [9]. The time and effort of caregiving are also 'spillover' effects of illness, but are included on the cost side of the CEA equation. While out-of-pocket expenses and time spent caregiving are relatively simple to quantify, assigning value to time is more daunting. Multiple valuation approaches have been proposed without clear guidance for a preferred method [17, 18]. Including informal time costs in CEA is becoming more common, although it is still the exception [17, 19]. This review focuses exclusively on QALY-related spillover effects, and readers are referred elsewhere for considerations of cost spillovers [17, 18].

This review presents health utilities associated with caregivers and family members of individuals with health conditions and diseases—including spillover utilities

and disutilities,² and caregiver and family member utilities, reported with and without comparator utilities. We also included preference-based, caregiver-specific utilities (i.e. spillover effects measured from the perspective of caregivers' experiences and including domains other than health), although these are not consistent with a QALY framework [20]. This compilation serves two functions. First, it provides a state-of-the-field overview of preference-based measures of caregivers' and family members' health-related quality of life, and second, it provides a catalog of the available data from which caregiver and family member QALYs may be derived to inform CEAs. Our primary goal for this review was to inform the inclusion of spillover effects in CEAs. Secondarily, we sought to advance the methods of spillover valuation and incorporation by expanding the collective knowledge base of measurement techniques, data, and, subsequently, evaluations that include spillover effects.

2 Methods

Our objective was to report the universe of articles that reported a preference-based measure of caregiver or family member spillover effects. We conducted a systematic review of the medical and economic literatures to identify articles containing utilities for family caregivers and non-caregiving family members, including three electronic databases: MEDLINE, EMBASE, and EconLit. We refined search terms by testing them against a set of known-to-us papers to ensure capture of relevant articles. The final search strategy combined terms describing utility measures with terms describing caregivers, family members, and burden: utility, disutility, preference weight, QALY, standard gamble, time trade-off, EuroQoL (EQ-5D), Short-Form 6-Dimension (SF-6D), Health Utilities Index (HUI), Quality of Wellbeing Scale (QWB), CarerQol, Carer Experience Scale (CES), Child Health Utility-9 dimensions (CHU-9D), and variants thereof; spillover, caregiver, family, partner, spouse, child, sibling, parent, grandparent, next of kin, burden, consequence, and associated variants. Figure 1 shows the search process (the full search specifications are included in the online supplementary material).

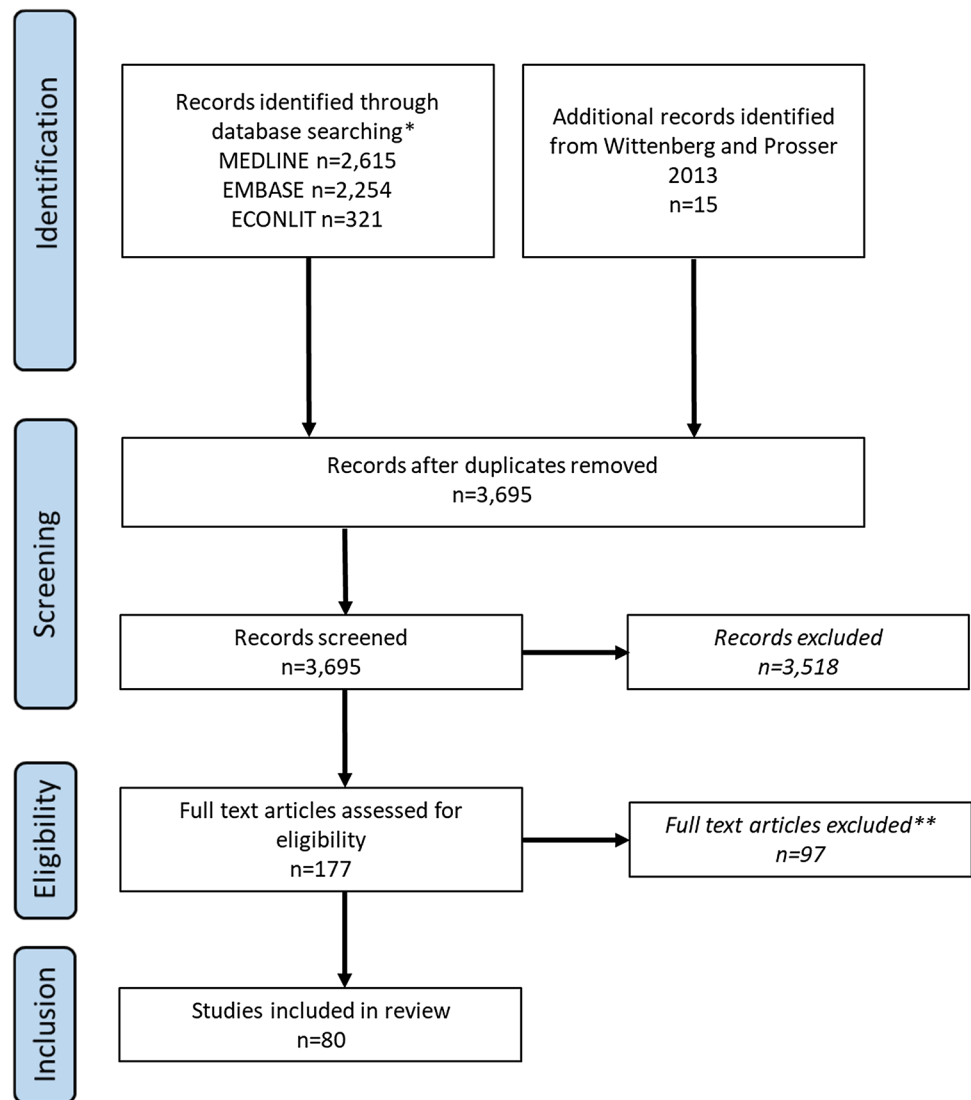
2.1 Eligibility Criteria

We included peer-reviewed articles published in English that reported a preference-based measure of caregiver or family member utility or disutility, including caregiver-focused measures for which population tariffs exist (i.e., CarerQol

¹ We use 'CEA' to include cost-utility analysis for ease of reading.

² Disutility is the utility loss associated with a particular state of health, as opposed to the utility of that state of health.

Fig. 1 PRISMA diagram of the search process. *Examples of search terms: [spillover, caregivers, family, partner, spouse, parent, child, sibling, grandparent, next of kin, burden, impact, consequences] AND [utility, disutility, preference weight, standard gamble, time trade-off, visual analog, QALY, SF-6D, EQ-5D, CarerQol, CES, HUI, QWB, CHU-9D]. **No caregiver or family member utility reported ($n = 75$); duplicate ($n = 12$); invalid score (utility reported > 1.0 or as WTP utility; $n = 4$); no English full-text available ($n = 4$); not peer-reviewed ($n = 2$). PRISMA Preferred Reporting Items for Systematic Reviews and Meta-Analyses, QALY quality-adjusted life-year, SF-6D Short-Form 6-Dimension, EQ-5D EuroQol-5 dimensions, CES Carer Experience Scale, HUI Health Utilities Index, QWB Quality of Wellbeing Scale, CHU-9D Child Health Utility-9 dimensions, WTP willingness to pay



[20] and CES [21]), from the inception of each database through 3 April 2018. We included articles that reported on multiple patient diseases and/or using multiple preference-based methods/instruments, but excluded articles that reported only the EQ-VAS or a visual analog scale measure unless the scores were transformed into utilities using a known algorithm [22].

We defined family member as anyone identified as having a familial relationship to the patient regardless of distance (e.g., cousins would meet our inclusion criterion). We assumed that all family members classified in articles as caregivers were such; we did not impose any criteria on this role. We included articles reporting on ‘informal caregivers’ unless they were described as exclusively non-familial, such as neighbors, church members, and the like, but excluded paid caregivers.

We included articles reporting on all patient diseases and conditions, including those that specified no disease, meaning they included caregivers regardless of the patient’s disease. We also included articles reporting on patient health states, defined as a distinct phase of a disease or condition (such as chemotherapy or hospitalization); a disease was defined as a diagnosed condition. We excluded disease transmission among family members from our definition of spillover effects. We included death as a health state when it was directly related to a disease or condition, such as maternal mortality, but we did not specifically search for bereavement. We imposed no age limit on patients or caregivers/family members.

We included articles reporting on studies specifically designed to measure spillover utility, those measuring caregiver/family member utility among other outcomes, and caregiver or patient interventions that included utility as an outcome. We excluded reviews, reports, study protocols,

commentaries, editorials, and conference papers, as well as articles that reported what appeared to be invalid utilities, such as scores > 1.0 or those described as ‘WTP utilities’.

2.2 Data Collection

After excluding duplicates, two authors (EW and LJ) independently screened titles and abstracts; conflicts were resolved by consensus. We repeated this process with the full-text articles remaining after screening. We recorded the reason for each exclusion using Covidence systematic review software (Veritas Health Innovation, Melbourne, VIC, Australia).

We extracted data that would allow a reader to identify potentially useful values for an analysis: patients’ disease/condition; patients’ age (adult/child/either); valuation measure used (EQ-5D, standard gamble, etc.); sample source (e.g., medical centers, patient association, population); country of sample; affected person’s role (i.e., family member/family caregiver/informal caregiver); caregiver/family member age (mean or other summary measure); sample size; utility (mean or median); if relevant to study design: comparison group source, sample size, and utility (mean or median); and if relevant, the reporting of utilities by strata, and other notes. We created a table entry for each patient disease/condition for which a relevant utility was reported in an article; articles that reported utility for more than one patient disease/condition were included in an entry for each. We included multiple utilities measured using different methods (e.g., HUI2 and HUI3) or applying different valuation weights for the same measure (e.g., Canadian and US weights for SF-6D) in one entry. If both caregiver/family member utilities and spillover disutilities were reported, we included each. If utilities were reported for the same condition/disease for multiple countries, we reported the one with the largest country-specific sample size. For all other instances of multiple utilities reported for the same disease/condition, we included those we deemed most salient to most readers and noted the availability of others in the ‘notes’ comment. We included the scores/values as reported by authors, but performed no manipulations or calculations on reported data. We grouped the entries into three categories: (1) spillover utilities or disutilities; (2) caregiver and/or family member utility reported with a matched or population comparison group; and (3) caregiver and/or family member utility reported alone.

3 Results

Our search yielded 5205 records. After removing duplicates, we screened 3695 studies by title and abstract, and assessed 177 full-text articles for eligibility; 80 articles remained for inclusion in our review (Fig. 1). Of these 80 articles, 8 (10%) reported spillover utility/disutility: 4 reported spillover disutility as the difference between population utility and the

observed family caregiver utility [23–26], 1 reported disutilities only [27], 1 reported both the difference between the observed caregiver utility and the population utility, as well as a utility for a hypothetical scenario in which the ill relative did not need caregiving [28], and 2 reported spillover utilities only, elicited using a direct method to isolate the spillover effect per se [29, 30]. Twenty-five (30%) reported a comparison group, either general population norms ($n = 9$; 3 of which also reported disutility) (Table 1) or matched, non-caregiver/family members or hypothetical scenarios’ utilities ($n = 16$) (Table 2). Fifty (63%) reported caregiver/family member utilities only (Table 3).³

Some articles reported utilities for multiple conditions or using multiple measurement methods, or for multiple strata of caregivers/family members. Across all 80 articles, Alzheimer’s disease and other types of dementia were the most frequent focus (15 articles), followed by cancer (6 articles) (Tables 1, 2, 3). Over half of the studies focused on caregivers/family members of ill adults (47, or 59%), 14 on ill children (18%), and the remainder focused on adults and children combined. The EQ-5D was the most common instrument used to measure caregiver/family member utility (58, or 69%, of uses among 84 in total; some articles reported multiple measurement methods). Indeed, 95% of articles used generic (i.e., indirect) measurement instruments: the SF-6D was used in 13 instances (16%), and the HUI and QWB were used three and two times, respectively. The caregiver-focused instruments (the CarerQol and CES) were used in seven instances (six uses and one use, respectively; 9%). Six articles (8%) reported caregiver/family member utility in the context of a patient and/or caregiver intervention trial. Most spillover effects research has been conducted in Europe (53 articles, 66%), followed by the US and Canada (20 articles, 25%). The earliest article reporting on this topic was published in 1988; nearly half (49%) were published between 2015 and 2018 (Tables 1, 2, 3).

4 Discussion

The past two decades have seen research on spillover health effects progress from a conceptual framework [15] to methods for measurement and incorporation into CEAs [14, 16, 27, 31, 32]. In 2016, the Second Panel on Cost-Effectiveness in Health and Medicine endorsed the inclusion of caregiver and family member effects in societal perspective CEAs, while at the same time acknowledging current limitations in measurement methodology and practice [9]. Dutch and National Institute for Health and Care

³ Multiple studies reported utilities for more than one disease/condition, each of which is represented in the tables as a separate entry.

Table 1 Literature reporting spillover utility loss or spillover utility

Author, year	Patient disease/condition	Patients' age (adult/child/ either)	Valuation measure ^a	Sample source	Country included in the sample	Affected person's role (family member, caregiver, etc.)	Caregiver/ family member age, years [mean (SD) unless otherwise specified]	Sample size	Spillover utility loss, or utility when noted [mean (SD) unless otherwise specified]	Comparison group source (if any)	Comparison group utility [mean (SD) unless otherwise specified]	Notes
Davidson et al., 2008 [28]	Any disease/condition	Adult-elderly	EQ-5D	EURO-FAMCARE study (six-country study of family caregivers)	Sweden	Family caregivers: partner, child	65.4	910	(a) -0.015 (b) -0.062			(a) Family caregiver utility minus age/sex-adjusted population mean (b) 'R-QALY' = family caregiver utility minus hypothetical scenario of family member in good health/not needing care Also reported at 12-month follow-up time point and by sex
Prosser et al., 2015 [27]	Arthritis	Adult	Standard gamble	Internet panel weighted to US population	US	Family members	18-29: 15.2% 30-44: 22.3% 45-59: 31.0% ≥ 60: 31.5% ^b	382	0.27 (0.25), median: 0.20 [IQR: 0.05-0.50]			1 minus respondent-reported utility for hypothetical family member of patient; also reported for cancer, dementia, depression
Prosser et al., 2015 [27]	Cancer: not specified	Adult	Standard gamble	Internet panel weighted to US population	US	Family members	18-29: 15.2% 30-44: 22.3% 45-59: 31.0% ≥ 60: 31.5% ^b	506	0.27 (0.25), median: 0.25 [IQR: 0.02-0.50]			1 minus respondent-reported utility for hypothetical family member of patient; also reported for arthritis, dementia, depression

Table 1 (continued)

Author, year	Patient disease/condition	Patients' age (adult/child/ either)	Valuation measure ^a	Sample source	Country included in the sample	Affected person's role (family member, caregiver, etc.)	Caregiver/ family member age, years [mean (SD) unless otherwise specified]	Sample size	Spillover utility loss, or utility when noted [mean (SD) unless otherwise specified]	Comparison group source (if any)	Comparison group utility [mean (SD) unless otherwise specified]	Notes
Basu et al., 2010 [30]	Cancer: prostate	Adult	Time trade-off (modified)	1 hospital	US	Family members: partner	57.7 (6.6)	26	Spillover utility: incontinence: 0.675 (0.344)			Utility for spillover effect of patient's health on spouse; also reported for impotence, post-prostatectomy, post-radiation therapy, 'watchful waiting', metastasis, and death
Poley et al., 2012 [24]	Congenital abnormality: ARM, CDH	Child	EQ-5D	1 hospital	Netherlands	Family caregivers: parents	Females: 35 [range 22–48] Males: 38 [range 24–59]	262	25- to 34-year-old mothers of child with ARM: -0.10	General population by age category	NS	Also reported as mean family caregiver utility (Table 2); all utilities reported by mother/father and age group (25–34 and 35–44 years)
Prosser et al., 2015 [27]	Dementia: Alzheimer's disease	Adult	Standard gamble	Internet panel weighted to US population	US	Family members	18–29: 15.2% 30–44: 22.3% 45–59: 31.0% ≥ 60: 31.5% ^b	206	0.25 (0.24), median: 0.21 [IQR: 0.02–0.50]			1 minus respondent-reported utility for hypothetical family member of patient; also reported for cancer, arthritis, depression
Prosser et al., 2015 [27]	Depression	Adult	Standard gamble	Internet panel weighted to US population	US	Family members	18–29: 15.2% 30–44: 22.3% 45–59: 31.0% ≥ 60: 31.5% ^b	541	0.26 (0.24), median: 0.20 [IQR: 0.02–0.50]			1 minus respondent-reported utility for hypothetical family member of patient; also reported for cancer, dementia, arthritis
Landfeldt et al., 2016 [43]	Duchenne muscular dystrophy	Child	EQ-5D	Disease network	Germany, Italy, UK, US	Family caregivers: parent	44 (8)	770	0.11	Population mean (age 35–44 years)	NS	Also reported as caregiver utility (Table 2), and by patient ambulation status, health status, and mental status

Table 1 (continued)

Author, year	Patient disease/condition	Patients' age (adult/child/ either)	Valuation measure ^a	Sample source	Country included in the sample	Affected person's role (family member, caregiver, etc.)	Caregiver/ family member age, years [mean (SD) unless otherwise specified]	Sample size	Spillover utility loss, or utility when noted [mean (SD) unless otherwise specified]	Comparison group source (if any)	Comparison group utility [mean (SD) unless otherwise specified]	Notes
Wittenberg et al., 2016 [29]	Opioid use/ treatment	Adult	Standard gamble	Nationally representative internet panel	US	Family members: spouse	18–24: 12.1% 25–44: 33.2% 45–64: 36.6% 65 +: 18.1% ^b	372	Spillover utility: active injection misuse 0.743, median 0.83 [IQR 0.510–1.0]			Utility for hypothetical spouse of individual in health state; also reported for active prescription misuse, methadone therapy, and buprenorphine therapy
Crawford et al., 2017 [26]	Otitis media: acute	Child	EQ-5D	3 hospitals	Malaysia	Family caregivers: parent	NS	110	(0.10) [range –0.07–0.55], median 0	Population norms (gender based)	NS	Also reported as caregiver utility (Table 3)
Brouwer et al., 2004 [25]	Rheumatoid arthritis	Adult	EQ-5D	Multicenter	Netherlands	Family caregivers: partner	61.5	145	0.0173 (0.2218)	General population (age- and sex-adjusted)	0.8035 (0.0586)	Also reported as mean caregiver utility (Table 2), and by caregiver sex, and patient quality of life

NCUtility and measurement methods of articles reporting preference-based measures of caregivers' and family members' health-related quality of life published in the medical and economic literatures from inception to April 2018, in alphabetical order by patient disease/condition

ARM anorectal malformation, CDH congenital diaphragmatic hernia, SD standard deviation, IQR interquartile range, NS not specified, EQ-5D EuroQoL-5 dimensions, US United States, UK United Kingdom; Comparison group sample size not included in any papers in this table.

^aEQ-5D refers to the 3-level version unless indicated as EQ-5D-5L

^bSurvey respondent age

Table 2 Literature reporting caregiver and/or family member utility and matched or population comparison group

Author, year	Patient disease/condition	Patients' age (adult/child/ either)	Valuation measure ^a	Sample source	Country included in the sample	Affected person's role (family member, caregiver, etc.)	Caregiver/family member age, years [mean (SD) unless otherwise specified]	Sample size	Utility [mean (SD) unless otherwise specified]	Comparison group source	Comparison group sample size	Comparison group utility [mean (SD) unless otherwise specified]	Notes
Matched comparison group													
Kuhlthau et al., 2010 [44]	Activity limitations	Child	EQ-5D	Medical Expenditures Panel Survey	US	Family caregivers: parents	<25: 3.7% 25–39: 51.8% 40–54: 39.4% 55+: 5.1%	2412	0.82	Parents of children without activity limitation	13,560	0.9	
Thomas et al., 2015 [45]	Any disease/condition	Either	EQ-5D	Population survey of primary care patients	UK	Informal caregivers	8 age categories reported, 18–85+	195,364	0.81	Non-caregivers	764,633	0.84	Sample is a population of primary care patients in England; also reported by no. of hours caregiving/week
Song et al., 2012 [46]	Cancer: 3–6 months after death	Adult	EQ-5D	33 palliative care centers	Korea	Family members: spouse, non-spouse	53.2 (12.5)	353	0.88 (0.2)	Non-bereaved family members	353	0.93 (0.13)	
Lee et al., 2015 [47]	Cancer	Either	EQ-5D	National survey	Korea	Family members	NS	3406	0.9225 (0.1278)	Non-cancer families	160,089	0.9411	Also reported by family member sociodemographic strata and perceived health status of the patient
Zhou et al., 2016 [48]	Death: maternal death due to pregnancy	Adult	EQ-5D	Childbirth records	China	Family members: husbands	Median: 33 [IQR 27–39]	84	Baseline: 0.73 (0.07) @ 1 year: 0.78 (0.07)	Families without a maternal death	96	Baseline: 0.82 (0.05) @ 1 year: 0.83 (0.04)	
Mohide et al., 1988 [37]	Chronic degenerative disorders	Adult	TTO	Visiting nurse agency and community service organization	Canada	Family caregivers	79.9 (10.9)	28	Caregivers of physically impaired: 0.795 Cognitively impaired: 0.412	Family members living with well elderly relatives	10	0.990	Instrument development study (CQLD); also reported for standardized caregiver wellbeing states: mild, moderate, severe
Gupta et al., 2012 [49]	Dementia: Alzheimer's disease	NS	SF-6D	Opt-in panel, weighted to population	US	Informal caregivers	52.51 (14.51)	1341	0.70 (0.14)	Non-caregivers	69,224	0.74 (0.14)	Also reported for multiple sclerosis (below)
Laks et al., 2016 [50]	Dementia: Alzheimer's disease and other	Adult	SF-6D	Opt-in internet panel, weighted to population	Brazil	Informal caregivers	42.09 (13.65)	209	0.682 (0.139)	Non-caregivers	10,644	0.715 (0.137)	

Table 2 (continued)

Author, year	Patient disease/condition	Patients' age (adult/child/ either)	Valuation measure ^a	Sample source	Country included in the sample	Affected person's role (family member, caregiver, etc.)	Caregiver/family member age, years [mean (SD) unless otherwise specified]	Sample size	Utility [mean (SD) unless otherwise specified]	Comparison group source	Comparison group sample size	Comparison group utility [mean (SD) unless otherwise specified]	Notes
Rochan-athimoke et al., 2018 [51]	Diarrhea: acute	Child	EQ-5D	3 hospitals	Thailand	Family caregivers: parent, grandparent (1 sibling)	NS	460	0.620 (0.12), median: 0.635 [IQR 0.514–0.694]	Same caregivers imagining child prior to hospital stay	460	0.964 (0.10), median: 1 [IQR 1–1]	Also reported by condition severity and whether diarrhea was rotavirus positive or negative
Brisson et al., 2010 [52]	Gastroenteritis (due to rotavirus)	Child	EQ-5D	59 outpatient practices	Canada	Family members: parents	NS	186	Baseline: 0.875 @ week 1: 0.945	Parent post-episode	186	@ week 2 0.967	Also calculated as QALY loss compared to end of episode (@ week 2)
Al-Janabi et al., 2016 [53]	Meningitis (long-term effects)	Either	EQ-5D-5L	Meningitis charity	UK	Family members	51 (13)	1053	0.87	Family members of meningitis patients with no after effects	517	0.91	
Gupta et al., 2012 [49]	Multiple sclerosis	NS	SF-6D	Opt-in survey panel, weighted to population	US	Informal caregivers	43.16 (15.80)	215	0.70 (0.15)	Non-caregivers	69,224	0.74 (0.14)	Also reported for dementia (above)
Acaster et al., 2013 [54]	Multiple sclerosis	Adult	EQ-5D	Patient recruitment panel	UK	Informal caregivers	50.88 (13.48)	200	0.74 (0.28)	Matched controls	200	0.82 (0.25)	
Gupta et al., 2015 [55]	Schizophrenia	Adult	SF-6D	Opt-in panel, weighted to population	France, Germany, Italy, Spain, UK	Informal caregivers	45.3 (15.8)	398	0.64 (0.12)	Non-caregivers	796	0.71 (0.13)	
Tilford et al., 2005 [4]	Spina bifida	Child	QWB	State birth defects surveillance system	US	Family caregivers: parents	37.7 (8.9)	98	0.76 (0.11) [range 0.54–1.0]	Families with a similar-aged child without spina bifida	49	0.80 (0.10) [range 0.59–1.00]	Also reported by location of lesion
Persson et al., 2017 [56]	Stroke (7 years post)	Adult	SF-6D	4 stroke units	Sweden	Family members: spouse	63 (11)	248	0.75 (0.12) [range 0.44–0.94]	Spouses of individuals who had not had a stroke	245	0.77 (0.11)	
Persson et al., 2017 [57]	Stroke	Adult	SF-6D	4 stroke units	Sweden	Family members: spouse	67 (8)	247	0.69 (0.12)	Spouses of individuals who had not had a stroke	245	0.77 (0.11)	Also reported for non-dependent stroke survivors

Table 2 (continued)

Author, year	Patient disease/ condition	Patients' age (adult/ child/ either)	Valuation measure ^a	Sample source	Country included in the sample	Affected person's role (family member, caregiver, etc.)	Caregiver/family member age, years [mean (SD) unless otherwise specified]	Sample size	Utility [mean (SD) unless other- wise specified]	Comparison group source	Compari- son group sample size	Comparison group utility [mean (SD) unless otherwise specified]	Notes
General population comparison group													
Nogueira et al., 2015 [58]	Alcohol dependence	Adult	SF-6D	Treatment program	Spain	Family caregivers: spouse, child, sibling	18–29; 6.3% 30–44; 29.7% 45–59; 39.1% 60–74; 20.3% 75+; 4.7%	64	0.724 (0.213), median: 0.758 [IQR 0.626– 0.868]	General popula- tion	600	0.807 (0.159), median: 0.874 [IQR 0.750–0.940]	
Sjoland et al., 2012 [59]	Cancer: advanced lung or gastroin- testinal, after diagnosis	Adult	EQ-5D	2 hospitals	Sweden	Family members: partners, children	63 (16)	36	@ 3 months post diagnosis: 0.73 (0.04); median: 0.8	General population (UK; 55–64 years age group)		0.80 (0.01)	Also reported by time after diagnosis, age, and relationship to patient
Poley et al., 2012 [24]	Congenital abnormality: ARM, CDH	Child	EQ-5D	1 hospital	Nether- lands	Family caregivers: parents	Females: 35 [range 22–48] Males: 38 [range 24–59]	262	25- to 34-year-old mothers of child with ARM: 0.83	General popula- tion by age category	NS	NS	Also reported as the differ- ence between caregiver and population mean (Table 1); all utilities reported by parent and age group (25–34 and 35–44 years)
Angelis et al., 2015 [60]	Cystic fibrosis	Either	EQ-5D-5L	Cystic Fibro- sis Trust	UK	Informal caregivers	37.3	33	0.836 (0.155)	General population age 35–44 years		0.91 (0.16)	
Landfeldt et al., 2016 [43]	Duchenne muscular dystrophy	Child	EQ-5D	Disease network	Germany, Italy, UK, US	Family caregivers: parent	44 (8)	770	0.81	Population mean (age 35–44 years)	NS	NS	Also reported as the difference between popula- tion mean and caregiver utility (Table 1), and by patient ambula- tion status, health status, and mental status
van Andel et al., 2011 [61]	Epilepsy	Adult	EQ-5D	1 medical center	Nether- lands	Family caregivers: partner, parent	52 [range 21–78]	86	0.88 (0.17)	Population	NS	0.88 (0.19)	
Kurien et al., 2017 [62]	Gastrostomy	Adult	EQ-5D	5 hospitals	UK	Informal caregivers	65 (12.2)	100	0.95 (0.15)	Population	200	0.93 (0.14)	Also reported 3 months post insertion

Table 2 (continued)

Author, year	Patient disease/condition	Patients' age (adult/child/ either)	Valuation measure ^a	Sample source	Country included in the sample	Affected person's role (family member, caregiver, etc.)	Caregiver/family member age, years [mean (SD) unless otherwise specified]	Sample size	Utility [mean (SD) unless otherwise specified]	Comparison group source	Comparison group sample size	Comparison group utility [mean (SD) unless otherwise specified]	Notes
Brouwer et al., 2004 [25]	Rheumatoid arthritis	Adult	EQ-5D	Multicenter	Netherlands	Family caregivers: partner	61.5	145	0.8203 (0.2229)	General population (age- and sex-adjusted)		0.8035 (0.0586)	Also reported as the difference between caregiver and population mean (Table 1); also reported by caregiver sex, and patient quality of life
van Exel et al., 2005 [63]	Stroke (6 months post)	Adult	EQ-5D	6 hospitals	Netherlands	Informal caregivers	60.0 (13.9)	135	0.83 (0.24) [range - 0.02 - 1.0]	General population (sex- and age-matched norms)		0.81	Also reported by caregiver burden

Utility and measurement methods of articles reporting preference-based measures of caregivers' and family members' health-related quality of life published in the medical and economic literatures from inception to April 2018, in alphabetical order by patient disease/condition

ARM anorectal malformation, CDH congenital diaphragmatic hernia, CLQI Caregiver Quality of Life Instrument, TTO time trade-off, SF-6D Short Form-6 Dimension, QWB Quality of Wellbeing Scale, NS not specified, IQR interquartile range, QALY quality-adjusted life-year, -EQ-5D EuroQol-5 dimensions, US United States, UK United Kingdom

^aEQ-5D refers to the 3-level version unless indicated as EQ-5D-5L

Table 3 Literature reporting caregiver and/or family member utility

Author, year	Patient disease/ condition	Patients' age (adult/child/ either)	Valuation measure ^a	Sample source	Country included in the sample	Affected person's role (family member, caregiver, etc.)	Caregiver/fam- ily member age, years [mean (SD) unless otherwise specified]	Sample size	Utility [mean (SD) unless otherwise specified]	Notes
Brouwer et al., 2006 [64]	Any disease/ condition	Adult	EQ-5D	Regional infor- mal care sup- port centers	Netherlands	Family caregivers: partner, parent, child	60.8 (13.1)	175	0.75 (0.21)	Instrument vali- dation study with primary data
Lutomski et al., 2015 [65]	Any disease/ condition	Adult	CarerQoL-7D	National data repository of research projects on older persons' health	Netherlands	Family caregivers: partner, child	63 (12)	3269	79.2 (14.7) ^b [range 14–98]	Compilation of data across studies; also reported by sampling frame subgroups: general popula- tion, hospital, and primary care settings
Bobinae et al., 2010 [35]	Any disease/ condition	NS	EQ-5D	Informal care support cent- ers	Netherlands	Informal caregivers	55.34 (12.37)	595	0.82 (0.20) [range -0.11– 1.0]	Distinguishes caregiving and caring about, but reported as combined utility
Brouwer et al., 2005 [7]	Any disease/ condition	Either	EQ-5D	Informal care support cent- ers	Netherlands	Family caregivers: partner, child, parent	60.2 (12.1) [range 17–90]	843	0.76 (0.23)	
del rio Lozano et al., 2017 [66]	Any disease/ condition	Either	EQ-5D-5L	Caregiver registries	Spain	Family caregivers: parents, chil- dren, spouses	59.83 (14.47)	610	0.828 (0.195)	Also reported by sex
Oldenkamp et al., 2017 [67]	Any disease/ condition	Adult-elderly	CarerQoL-7D	National data repository of research projects on older persons' health	Netherlands	Family caregivers: spouse, child	64.6 (12.61)	660	Baseline: median: 83.10 ^b [IQR 73.9–89.6] @ 12 months: median: 80.42 [IQR 74.0–90.0]	
Hoefman et al., 2014 [68]	Autism spec- trum disorder	Child	ED-5D, SF-6D	2 autism treat- ment network registries	US	Family caregivers: parents (mostly mothers)	39.4 (8.3)	224	EQ-5D: 0.85 (0.14) SF-6D: 0.74 (0.12)	

Table 3 (continued)

Author, year	Patient disease/ condition	Patients' age (adult/child/ either)	Valuation measure ^a	Sample source	Country included in the sample	Affected person's role (family member, caregiver, etc.)	Caregiver/fam- ily member age, years [mean (SD) unless otherwise specified]	Sample size	Utility [mean (SD) unless otherwise specified]	Notes
Khanna et al., 2013 [69]	Autism spec- trum disorder	Child	EQ-5D	Autism network	US	Family caregivers: parents (mostly mothers)	NS	316	0.82 (0.16)	Psychometric study; also reported by disease severity
Khanna et al., 2013 [70]	Autism spec- trum disorder	Child	EQ-5D	Autism network	US	Family caregivers: parents (mostly mothers)	NS	316	Female caregivers: 0.81 (0.16)	Also reported for male caregivers, younger/older caregivers
Vrettos et al., 2012 [71]	Cancer: during chemotherapy	Adult	EQ-5D	1 hospital	Greece	Family caregivers: spouses, parents, children	48.9 [range 20–80]	212	Females: 0.783 (0.228) Males: 0.895 (0.141)	
Bradshaw et al., 2013 [72]	Cognitive impairment	Adult-elderly	EQ-5D	Acute general hospital wards	UK	Family caregivers: spouse, child, other	Median: 62 [IQR 56–73]	180	Median: 0.8 [IQR 0.62– 1.0]	Also reported by caregiver/ patient living situation
Payakachat et al., 2011 [73]	Craniofacial malforma- tions	Child	HUI3, SF-6D, QWB	State monitor- ing study sample	US	Family members	31.9 (5.3) [range 23.2–45.7]	65	HUI3: 0.84 (0.23) [range –0.18– 1.0] SF-6D: 0.81 (0.13) [range 0.51– 1.0] QWB: 0.67 (0.14) [range 0.29– 1.0]	
Chevreul, 2016 [74]	Cystic fibrosis	Either	EQ-5D	Cystic fibrosis associations, registries	Bulgaria, France, Germany, Hungary, Italy, Spain, Sweden, UK	Informal caregivers	34.5 (5.8)–42.9 (8.0) across countries	271 total; 56 Spain	Spain: 0.919 (0.086)	Reported by country
Chevreul et al., 2015 [75]	Cystic fibrosis	Either	EQ-5D-5L	Cystic fibrosis associations	France	Informal caregivers	NS	40	0.761	Also reported by disease dura- tion

Table 3 (continued)

Author, year	Patient disease/ condition	Patients' age (adult/child/ either)	Valuation measure ^a	Sample source	Country included in the sample	Affected person's role (family member, caregiver, etc.)	Caregiver/fam- ily member age, years [mean (SD) unless otherwise specified]	Sample size	Utility [mean (SD) unless otherwise specified]	Notes
Fitzgerald et al., 2018 [76]	Cystic fibrosis	Child	CareerQoL-7D	National cohort study of cystic fibrosis	Ireland	Family caregivers: parents	Mothers: 35.5 (4.9) Fathers: 38.0 (5.5)	195	Mothers: 84.7 ^b [IQR 74.5–88.0] Fathers: 89.2 [IQR 79.6–96.5] 70.1 ^b (19.7) [range 5–100]	Also reported by child age
Krajo et al., 2014 [77]	Dementia: not specified	Adult	CareerQoL-7D	Patient regis- tries	Netherlands	Family caregivers: partners and parents	66.4 (13.4) [range 29–93]	223		
Bell et al., 2001 [78]	Dementia: Alzheimer's disease	Adult	HUI2	13 community and institu- tional care sites	US	Informal caregivers	63	679	0.87 (0.11)	Also reported by disease severity and recruit- ment setting
Fang et al., 2016 [79]	Dementia: Alzheimer's disease	Adult	EQ-5D	9 clinics	Canada	Caregivers	Median: 69 [IQR 59–77]	216	UK weights: 0.8 Canadian weights: 0.83	Reported using UK and Canadian valu- ation sets; also reported by disease severity
Majoni and Oremus, 2017 [80]	Dementia: Alzheimer's disease	Adult	EQ-5D	9 clinics	Canada	Informal caregivers	Retired median: 74 [IQR 68–80] Employed median: 56 [IQR 51–62]	200	Retired median: 0.8 [IQR 0.73– 1.0] Employed median: 0.84 [IQR 0.83– 1.0]	Reported separately for retired and employed caregivers
Neumann et al., 2000 [81]	Dementia: Alzheimer's disease	Adult	HUI2 and HUI3	13 community and institu- tional care sites	US	Caregivers	63 (14)	679	HUI2: 0.87 (0.18) HUI3: 0.87 (0.14)	Also reported by disease severity

Table 3 (continued)

Author, year	Patient disease/ condition	Patients' age (adult/child/ either)	Valuation measure ^a	Sample source	Country included in the sample	Affected person's role (family member, caregiver, etc.)	Caregiver/fam- ily member age, years [mean (SD) unless otherwise specified]	Sample size	Utility [mean (SD) unless otherwise specified]	Notes
Oremus et al., 2014 [82]	Dementia: Alzheimer's disease	Adult	EQ-5D	Memory and geriatric clinics	Canada	Informal caregivers	Median: 69 [IQR 59–77]	216	US weights: 0.85, median: 0.83 [IQR 0.79–1.0] Canadian weights: 0.80, median: 0.83 [IQR 0.74– 0.89]	Reported using US and Cana- dian valua- tion sets; also reported by disease severity
Reed et al., 2017 [83]	Dementia: Alzheimer's disease	Adult	EQ-5D	Memory clinics	France, Germany, UK	Informal caregivers	67.3 (12.0)	1495	0.84 (0.2), median: 0.89 [IQR 0.79– 1.0]	Also reported by disease severity
Dahrup et al., 2014 [84]	Dementia: not specified	Adult–elderly	EQ-5D	Social service agencies	Sweden	Family caregivers	Intervention median: 62 [IQR 27–90] Control median: 62 [IQR 38–95]	308	Intervention median: 0.848 [IQR 0.725–1.0] Control median: 0.796 [IQR 0.725– 1.0]	Caregiver inter- vention trial; also reported by patient living situation and relation- ship with patient
Knapp et al., 2013 [85]	Dementia: not specified	Adult	EQ-5D	4 service settings	UK	Family caregivers	NS	260	Usual treat- ment: 0.77 (0.23) Intervention: 0.77 (0.22)	Caregiver inter- vention trial; also reported at follow-up period
Orrell et al., 2017 [86]	Dementia: not specified	Adult	EQ-5D	8 care centers and disease associations	UK	Informal caregivers	NS	273	Intervention: 0.82 Control: 0.76	Patient and caregiver inter- vention trial; also reported at mid-way point in trial
Stewart et al., 2005 [87]	Dementia: not specified	Adult–elderly	EQ-5D	Social services and occupa- tional therapy sites	UK	Informal caregivers	NS	80	Arm 1: 0.69 (0.28) Arm 2: 0.77 (0.21)	Patient and caregiver intervention trial, two arms; also reported at follow-up

Table 3 (continued)

Author, year	Patient disease/ condition	Patients' age (adult/child/ either)	Valuation measure ^a	Sample source	Country included in the sample	Affected person's role (family member, caregiver, etc.)	Caregiver/fam- ily member age, years [mean (SD) unless otherwise specified]	Sample size	Utility [mean (SD) unless otherwise specified]	Notes
Vroomen et al., 2016 [88]	Dementia: not specified	Adult	EQ-5D	Case manage- ment clients	Netherlands	Informal caregivers	Intervention 1: 64.5 (12.8) Intervention 2: 64.4 (12.4) Controls: 65.8 (11.7)	521	Intervention 1: 0.8 (0.2) Intervention 2: 0.9 (0.2) Controls: 0.9 (0.2)	Patient/caregiver intervention trial
Tiberg et al., 2016 [89]	Diabetes: type 1	Child	SF-6D	1 hospital	Sweden	Family caregivers: parents	Control: moth- ers: 40.4 (5.3); fathers: 43.6 (6.6); Intervention: mothers: 40.1 (6.2); fathers: 42.6 (5.7)	76	Control: 0.775 Intervention: 0.811	Patient interven- tion trial; also reported separately at discharge and three follow-up time points
Campbell et al., 2018 [90]	Dravet syn- drome	Child	EQ-5D-5L	1 hospital	US	Informal caregivers	NS	30	0.78 (0.17) [range 0.31–1]	Also reported by country
Cavazza et al., 2016 [91]	Duchenne muscular dystrophy	Either	EQ-5D	Patient organi- zations	Bulgaria, France, Germany, Hungary, Italy, Spain, Sweden, UK	Informal caregivers	25.0–49.6 across coun- tries	154	Across coun- tries: 0.71	
Chevreur et al., 2016 [92]	Fragile X syndrome	Either	EQ-5D	Patient asso- ciations and registries	France, Hungary, Italy, Spain, Sweden, UK	Family caregivers: parent, other	37.5 (7.0)–47.9 (11.8) across countries	110 total (56 France)	France: 0.754 (0.239)	Reported by country
Chevreur et al., 2015 [93]	Fragile X syndrome	Either	EQ-5D-5L	Patient associa- tions	France	Informal caregivers	NS	NS	0.75 (0.24)	Also reported by patient age
Agren et al., 2013 [94]	Heart failure	Adult	SF-6D	2 hospitals	Sweden	Family caregivers: partner	Intervention: 67 (12) Controls: 70 (10)	109	Intervention group: 0.7112 Controls: 0.7096	RCT of interven- tion for patient/ partner dyads; also reported at 12-month follow-up

Table 3 (continued)

Author, year	Patient disease/ condition	Patients' age (adult/child/ either)	Valuation measure ^a	Sample source	Country included in the sample	Affected person's role (family member, caregiver, etc.)	Caregiver/fam- ily member age, years [mean (SD) unless otherwise specified]	Sample size	Utility [mean (SD) unless otherwise specified]	Notes
Iqbal et al., 2010 [95]	Heart failure	Adult	EQ-5D	1 academic hospital	NS	Informal caregivers		131	0.76 (0.03)	Also reported by caregiver sex, patient quality of life
Squire et al., 2017 [96]	Heart failure	Adult	EQ-5D-5L and CES	5 care centers	England	Family caregivers	69 [range 43–88]	72	EQ-5D: 0.75 (0.18), [range 0.28–1.0], median: 0.77 CES 39 (20), median 38 ^b	
Cavazza et al., 2016 [97]	Hemophilia	Either	EQ-5D	Patient associa- tions	Bulgaria, France, Germany, Hungary, Italy, Spain, Sweden, UK	Family caregivers: parent, partner	34.7 (8.6)–48.0 (19.8) across countries	62	Across coun- tries: 0.87 (0.15)	Also reported by country
Al-Janabi et al., 2017 [98]	Meningitis (long-term effects)	Either	EQ-5D-5L	Meningitis charity	UK	Family caregivers: parent, partner, grandparent	52.9 (11.7)	497	0.84 (.20)	
Bhadhuri et al., 2017 [39]	Meningitis (long-term effects)	Either	EQ-5D-5L, SF-6D	Meningitis charity	UK	Family caregivers and non-caregiving family mem- bers	Caregivers: 45.9 (11.9) Non-caregiving family mem- bers: 51.2 (12.1)	648	Caregivers: 0.80 (0.20) Non-caregiving family mem- bers: 0.85 (0.19)	Also reported for SF-6D and by patient improvement and hours of care provided
Hastrup et al., 2011 [99]	Mental Illness	Either	EQ-5D	Informal caregivers' regional sup- port centers	Netherlands	Informal caregivers	59.92 (13.22)	865 total	0.73 (0.24)	Comparison of mental illness to somatic illness; also reported for somatic illness (below) and both co-occur- ring

Table 3 (continued)

Author, year	Patient disease/ condition	Patients' age (adult/child/ either)	Valuation measure ^a	Sample source	Country included in the sample	Affected person's role (family member, caregiver, etc.)	Caregiver/fam- ily member age, years [mean (SD) unless otherwise specified]	Sample size	Utility [mean (SD) unless otherwise specified]	Notes
Péntek et al., 2016 [100]	Mucopolysac- charidosis	Either	EQ-5D	Patient organizations	Bulgaria, France, Germany, Hungary, Italy, Spain, Sweden	Informal caregivers	21.5 (29.0)– 47.3 (5.6) across coun- tries	66	Italy: 0.681 (0.383)	Reported by country
Crawford et al., 2017 [26]	Otitis media: acute	Child	EQ-5D	3 hospitals	Malaysia	Family caregivers: parent	NS	110	0.92 (0.10), [range 0.38– 1.0]; median: 0.94	Also reported as difference between population norms and caregiver util- ity (Table 1)
Hoefman et al., 2015 [101]	Palliative care	Adult	EQ-5D, CarerQol-7D, CES	1 service pro- vider	Australia	Family caregivers: partner, parent	62.3 (11.9)	97	EQ-5D: 0.7 (0.2) CarerQol: 73.5 ^b (17.1) CES: 72.5 ^b (16.3)	
Carod-Artal et al., 2013 [102]	Parkinson's disease	Adult	EQ-5D	1 hospital outpatient clinic	Brazil	Family caregivers: spouse, child	55.7 (13.1)	50	0.7 (0.3) [range –0.031–1]	
Martinez- Martin et al., 2007 [103]	Parkinson's disease	Adult	EQ-5D	7 medical centers	Spain	Family caregivers: spouse, child	61.3 (13.2) [range 30–85]	78	0.8 (0.2) [range 0.2–1]	
Martinez- Martin et al., 2008 [104]	Parkinson's disease	Adult	EQ-5D	Specialized practices	Spain	Family caregivers: spouse, child	59.4 (13.5) [range 25–87]	286	0.79 (0.24) [range –0.15– 1.0]	
Chevreur et al., 2016 [105]	Prader-Willi syndrome	Either	EQ-5D-5L	Patient associations	France	Informal caregivers	NS	16	0.74 (0.25)	Also reported by patient age: child and adult
van Dam et al., 2017 [106]	Rehabilitation: following geriatric reha- bilitation	Adult	CareQol-7D	16 skilled nursing facili- ties	Netherlands	Family caregivers: partner, child	63 (13.3)	350	Median: 83.9 ^b [IQR: 74.4– 91.7]	

Table 3 (continued)

Author, year	Patient disease/ condition	Patients' age (adult/child/ either)	Valuation measure ^a	Sample source	Country included in the sample	Affected person's role (family member, caregiver, etc.)	Caregiver/fam- ily member age, years [mean (SD) unless otherwise specified]	Sample size	Utility [mean (SD) unless otherwise specified]	Notes
Daltio et al., 2017 [107]	Schizophrenia	Adult	SF-6D	1 hospital	Brazil	Family caregivers: parent, partner, child	56.05 (12.99)	159	0.78 (0.08)	Willingness- to-pay study; utility collected as a descriptive variable
Hastrup et al., 2011 [99]	Somatic illness (unspecified)	Either	EQ-5D	Informal caregivers' regional support cent- ers	Netherlands	Informal caregivers	59.78 (11.86)	865 total	0.78 (0.22)	Comparison of mental illness to somatic illness; also reported for mental illness (above) and both co-occur- ring
Cramm et al., 2012 [108]	Stroke	Adult	EQ-5D	9 stroke service facilities	Netherlands	Family caregivers: partner, child, sibling	59.14 (14.87)	251	0.74 (0.34)	
Carod-Artal et al., 2009 [109]	Stroke	Adult	EQ-5D	1 clinic	Brazil	Family caregivers: spouse, children, other family	42.0 (14.1)	200	0.7 (0.2) [range 0.04–0.85]	Also reported by relationship to patient and patient's func- tional status
Chevreur et al., 2015 [110]	Systemic sclero- rosis (sclero- derma)	Adult	EQ-5D-5L	Patient associations	France	Informal caregivers	NS	14	0.66 (0.41)	

Utility and measurement methods of articles reporting preference-based measures of caregivers' and family members' health-related quality of life published in the medical and economic litera-
tures from inception to April 2018, in alphabetical order by patient disease/condition

IQR interquartile range, *NS* not specified, *SF-6D* Short Form-6 dimensions, *EQ-5D* EuroQol-5 dimensions, *CES* Carer Experience Scale, *HUI* Health Utilities Index, *QWB* Quality of Wellbeing
Scale, *CI* confidence interval, *RCT* randomized controlled trial, *US* United States, *UK* United Kingdom

^aEQ-5D refers to the 3-level version unless indicated as EQ-5D-5L

^bCarerQol and CES reported on a 0–100 scale

Excellence (NICE) guidelines also recommend inclusion of spillover effects [10, 11]. This systematic review facilitates adherence to current recommendations by providing a catalog of preference-based values for spillover effects available to date. It is broader and more comprehensive than a previous review that focused on spillover utility only; this review includes caregiver and family member utilities from which spillover can be estimated or derived, and preference-based measures of caregiving effects beyond health [13]. Spillover costs for informal care are also recommended for inclusion, and have been reviewed and discussed elsewhere [17, 18].

Along with this catalog and the opportunity to incorporate spillover effects into CEAs come a host of questions, all of which have practical and policy implications: what is and is not considered spillover by different investigators; how can and cannot spillover be captured using different measures and populations; and how and under what circumstances it should or should not be included in CEAs.

4.1 What is Spillover and How can it be Measured?

‘Spillover’ results from caregiving, simply caring about others, or a combination of the two. What constitutes caregiving for one person may be ordinary behavior for another—the distinction, for example, between ‘regular’ parenting and caregiving for sick children [33]. Caregiving is often shared among family members, it sometimes vacillates between family and paid caregivers (such as when patients cycle between home and hospital), and it changes in nature and intensity over time [34]. Caregiving can provide sustenance to family members who might otherwise feel a lack of control or disengaged from an ill relative, moderating the otherwise burden of care [5]. While the literature tends to focus on primary caregivers, other family members both provide care and experience spillover effects of illness [5, 35]. The inconsistent description of caregiving and family involvement in the literature injects variability into both the estimation of spillover QALYs and how to interpret the policy implications of family-based CEAs.

Health utility scores can capture the health-related spillover effects of caregivers and family members if the health-specific spillover effects are isolated; meaning, the utility associated with solely the caring for or caring about component of having an ill relative. These utility scores can be used to calculate QALYs for CEAs. Care-related measures, such as the CarerQOL, albeit preference-based, include non-health domains in addition to health, and as such are incompatible with CEAs. However, utility scores that reflect only the change in health-related quality of life (HRQOL) associated with spillover are available for just a small set of conditions, therefore other measures of

caregiver/family member effects may yield values suitable for use in CEAs when certain assumptions hold.

Most articles in this review fall into the category of conventionally-defined health utility scores: the utility of a caregiver or non-caregiving family member of an ill relative. These scores may include the impact of spillover but also the underlying health of the individual. Elderly caregivers, for example, are likely to have chronic health conditions simultaneous with their caregiving responsibilities, therefore their utility scores will reflect a combination of both effects. In some of these articles, utilities are reported for a matched sample, such as non-caregivers or family members of healthy individuals, or from general population norms, allowing for the calculation of a ‘spillover utility’. In the majority of articles reviewed, however, a comparison group utility is not reported, but an analysis could use an appropriate population norm to derive a spillover utility, carefully considered to match the demographics of the caregiver sample. The underlying assumption in this literature is that spillover effects are additive, yet this has not been empirically demonstrated; interaction effects have been hypothesized [30]. While a growing supply of spillover utility data is available in the literature, much of it requires assumptions such as this to be able to use these utilities in a CEA. A further challenge is that the current literature rarely distinguishes between caring for and caring about effects, which may be difficult to disentangle.

Caregiver-focused ‘utility equivalents’ are preference-based but are distinct from QALYs. These measures—the CarerQOL and CES—include a different and more comprehensive set of dimensions than are typically included in QALY-based measures (e.g., fulfillment, financial problems, relational problems). While they may accurately capture caregiver-relevant dimensions [36], their valuations are based on a care-related quality-of-life scale so cannot be used to estimate QALYs, and therefore can neither be combined with patient QALYs in CEAs nor compared with CEAs based on QALYs [20]. They are of particular value, however, for comparatively evaluating caregiver interventions. An early prototype of a caregiver-specific measure that was QALY-based but focused on caregiver-relevant dimensions—the Caregiver Quality of Life Index (CGLI)—was largely supplanted by these instruments [37].

4.2 How and Under What Circumstances Should Spillover be Included in Cost-Effectiveness Analyses?

Incorporation of spillover effects into CEAs faces significant methodological questions, including concerns regarding prioritizing caregiver health over patient health, equity in decision making, and ‘double counting’ of benefits. At the most basic level, spillover and patient QALYs can be

summed to arrive at total QALYs, and this is currently the most common approach observed in practice. Some have proposed a weighting factor be applied to adjust for the relative importance of spillover effects compared with changes in health for the primary patient [14]. In the extreme, including spillover QALYs could tilt decisions toward benefiting caregivers/family members over the patient, although this is not the intended purpose of considering these effects [38]. Whose QALYs to include in spillover is also an unanswered question as evidence suggests effects extend beyond the primary caregiver [39] and perceptions of relevance (i.e. ‘closeness’) vary across individuals [40]. The articles in this review provide the data to inform family-based CEAs but do not inform the questions underlying appropriate incorporation approaches.

Equity issues are significant in including spillover effects in CEAs. If spillover is included, cost-effectiveness ratios for interventions targeting diseases/conditions that require caretaking and/or negatively affect family members could be favored over diseases/conditions that do not. Interventions that affect oftentimes isolated patients, such as homeless individuals, could be undervalued relative to those that affect more connected individuals, such as children. At the same time, not including spillover could result in policy decisions that disregard the interests of caregivers and families [38, 41]. While it might be sensible to consider the effect of pediatric conditions on parents as well as the child, as successful treatment confers benefits on both, in cases such as dementia, patients’ and families’ interests may at times be at odds: successful treatment may prolong the patient’s life and extend the caretaking burden for the family. Including spillover QALYs in CEAs is both a methodological decision, including the ‘what’ and ‘how’ aspects, and a normative decision, including the ‘if’ and ‘when’ aspects. Whether it is normatively justifiable to include spillover in economic evaluation recognizing the potential reallocation of resources that may ensue is as yet unresolved [38, 41]. It is clear, however, that including spillover necessitates the accurate and normative definition of ‘who qualifies’, as who is or is not included can have an impact on the results, regardless of how those results are used in policy.

Another concern raised with regard to including spillover in CEAs is double counting: spillover effects may already be implicitly included in utilities. Patients’ anxiety or depression, for example, may be a function of their condition’s effect on their family, rather than or in addition to its effect on themselves, indicating that family spillover may be at least in part reflected in patient utilities. Moreover, it may be difficult for caregivers or family members to disentangle their health from their ill relative’s, therefore their ‘spillover’ utility may include more than the effect on themselves individually. Although reasonable concerns, difficulty in measurement ought not preclude the incorporation of an endorsed

component of effects. Advances in measurements, most of which use direct utility elicitation methods, have been made to attempt to accurately capture spillover independently, although with unconfirmed success [27, 28, 30]. Judicious use of sensitivity analysis may be a reasonable approach for the time being to minimize the effect of potential measurement error on CEA results.

4.3 Study Limitations

Considerations should be noted regarding our review. While our search is comprehensive as of our end date, articles including utilities for spillover effects are being published with increasing frequency [19], and will soon render our catalog incomplete. We are in the process of developing an online, open-access repository of spillover effect utilities, which will be updated regularly as a public resource. Moreover, our catalog excludes the gray literature or unpublished sources. Unpublished utilities that are in the pipeline, via conference presentations and abstracts, will likely find their way into the published literature in the future and will be incorporated into successive versions of the catalog. Publication bias is not a concern for this review because our results are descriptive and not intended for inference. We limited the data included in our tables to ensure accessibility for readers—essentially a size that was viewable on a standard size page or computer screen—therefore details that are important to some may have been omitted. Finally, we made subjective judgments about the relative salience of utilities in articles reporting multiples, but describe others in the ‘notes’ section of the tables.

5 Conclusions

The scope of CEAs is expanding from patient-based analyses to caregiver/patient dyadic and family-based analyses. While this expansion is consistent with theoretical principles of maximizing health benefits, prevailing methodological consensus, and demographic and health system changes, it raises practical challenges for CEA and highlights data gaps. It is likely, at least for the time being, that QALYs are here to stay [42]. Caregiver and family member spillover effects will therefore be primarily measured in QALYs and will consequently require utilities. This review provides a catalog of utilities to facilitate the calculation of QALYs and inform CEAs. Additional research is needed on methods of measuring and incorporating spillover QALYs to promote, among other things, an accurate reflection of societal preferences for caregiver/family effects relative to patients’ effects. It is our goal to advance the inclusion of spillover in CEA by providing this accessible overview of the spillover effects of HRQOL literature. We also aspire to expand the knowledge

base of spillover-based CEAs, from which we will answer these remaining questions.

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Data Availability All data used in this study are publicly available in the form of published journal articles. The summary data included in the tables are extracted directly from the articles. All data are therefore reported directly in the paper or available to the public.

Compliance with Ethical Standards

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Conflict of interest Eve Wittenberg, Lyndon James, and Lisa Prosser have no conflicts of interest to report.

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