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Systematic Literature Review

How Do Patients With Type 2 Diabetes Mellitus Value the Importance of Outcomes? An Overview of Reviews

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ABSTRACT

Objectives: We aimed to assess how patients value the importance of type 2 diabetes mellitus (T2DM) related outcomes.

Methods: Overview of systematic reviews (SRs) reporting patients' utilities or disutilities for T2DM outcomes. We searched 3 databases from inception until June 2021. Study selection and data extraction were conducted in pairs. We evaluated the quality of SRs with the Joanna Briggs Institute Checklist, and the overlap with the corrected covered area. We estimated descriptive statistics, and, when possible, conducted metanalysis.

Results: We identified 11 SRs, including 119 studies and 70 outcomes. Most reviews were high-quality SRs. The outcomes with the lowest utilities were hypoglycemia with very severe symptoms (acute complications), stroke (macrovascular complications), diabetic peripheral neuropathy with severe pain (microvascular complications), extreme obesity (comorbidities), and insulin only or combined (management of diabetes). Good/excellent glucose control and noninsulin injectable showed higher values than T2DM without complications. The outcomes with the highest disutilities were amputation, depression, major hypoglycemia, stroke, and management using only insulin.

Conclusions: We provide standardized, reliable utility values (or associated disutilities) for T2DM, acute, microvascular and macrovascular complications, related comorbidities and treatments that may support judgments when making clinical recommendations, designing decision support tools, and developing interventions and economic analysis.

Keywords: health utility values, metanalysis, overview, patients preferences, type 2 diabetes mellitus.

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Introduction

The prevalence of type 2 diabetes mellitus (T2DM), which accounts for 90% to 95% of all diabetes, has increased globally over the past few decades.[1-3] T2DM represents a significant economic burden to society, health systems, and patients, mainly directly affecting low and middle-income countries.[4-6] Moreover, at an individual level, it is associated with reduced life expectancy, significant morbidity, and diminished quality of life.[1]

High-quality care in T2DM[6] often requires complex, multifaceted interventions, where it is essential to determine under what circumstances an intervention can be recommended and implemented. A fundamental component of evidence-based medicine is the integration of patients' values and preferences with the best available evidence in decision-making processes.[7] Patients' values and preferences represent the importance placed on the outcomes.[8] In healthcare decision-making processes, empirical evidence of patients' values and preferences is not often available. Instead, this information can be derived from the judgment of healthcare providers or expert panels.

The importance of outcomes can be obtained from quantitative utility-based measures. Utility values reflect a judgment on the desirability of a particular outcome and are anchored on a scale from 0 (dead) to 1 (optimal health) but can have negative values (worse than death). Disutility represents the decrement in utility because of a specific symptom or complication and is often expressed as a negative value representing the impact of the symptom or disease compared with a reference utility value (eg, people who do not experience the event).[9-11] Utilities and disutilities can derive from (1) direct methods such as matching methods (ie, standard gamble [SG], time trade-off [TTO], or rating scales), conjoint analysis (ie, discrete-choice experiments [DCEs], contingent valuation and willingness to pay, probability trade-off, and paired comparison); or (2) indirect methods using multiattribute quality of life instruments, such as the EQ-5D, the Short Form-6-Dimension (SF-6D), or the Health Utilities Index (HUI-3). Responses are converted to utilities using "tariffs" or "weights." derived from previous exercises in which various possible outcomes have been calibrated using trade-off techniques from a sample of the general population.[8] Moreover, disutility values can derive from different analysis models.

Currently, there is a growing interest in assessing patients' values and preferences and developing systematic reviews (SRs) estimating utilities and nonutility measures of how patients value the importance of outcomes.[12-15] A technique to summarize a body of evidence from SRs is to conduct an overview of SRs. An overview of SRs of quantitative utility-based measures on T2DM outcomes would be valuable to inform decision-making processes in T2DM. Therefore, we aimed to assess how patients value the importance of T2DM-related outcomes.

Methods

We conducted an overview SRs.[16,17] The methodological details are summarized below, and further details are available in the protocol (in PROSPERO, a database of prospectively registered systematic reviews, CRD42019117867).[18] We adopted the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement for reporting.[19]

Eligibility Criteria

Type of reviews

SRs of quantitative studies reporting the following: (1) a systematic search (at least in 1 database), (2) a list of primary studies, and (3) a description of the type of analysis/methodology used.

The phenomenon of interest

SRs of studies assessing how patients with T2DM value the importance of outcomes.

Population

Adult patients (≥18 years old) with T2DM. SRs including >1 disease or type of population were included if primary studies included at least 80% of adults with T2DM or if results were reported disaggregated. We excluded reviews which focused only on type 1 diabetes mellitus (T1DM), children, or gestational diabetes.

Outcomes

Utility or disutility measures derived from patients with T2DM using direct or indirect methods[8] regarding T2DM-related outcomes, including T2DM diagnosis, experiencing a specific symptom, an acute or chronic complication, or treatment modality.

Context/setting and language

No geographical or setting restrictions, except those confined to inpatient care. We included studies published in English only.

Search strategy

We designed and executed a literature search strategy in MEDLINE (accessed through PubMed), the Cumulative Index of Nursing and Allied Health Literature, and PsycINFO from inception to November 2020. The search was updated monthly using each database's alert system until June 2021. The search included a sensitive content search strategy previously published[20] and specific terms for T2DM. We limited our search to SRs by applying methodological filters in each database. Additionally, we conducted a forward citation of elected SRs in Scopus. The search strategy is available in Appendix Table 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2023.07.003.

Study selection

After achieving at least 80% of agreement of an initial calibration exercise (with 10% of the references), a pair of authors (J.B. and C.R.C.) screened titles and abstracts, with a subsequent independent full-text assessment. Disagreements were solved by discussion or with the help of a third author (E.N.D.G). We managed references with Endnote X9.

Data collection

After pilot-testing the data extraction form, 1 author (J.B.) extracted data from SRs, including their additional materials, and 2 authors cross-checked it for accuracy (E.N.D.G. and A.V.M.). We collected the following: (1) general and methodological characteristics of SRs and included primary studies, (2) country, context, and setting of primary studies (eg, clinical trial), (3) participants or sample characteristics (eg, number of participants, sex, age, disease severity, comorbidities), and (4) outcomes with their utility or disutility measures (mean and variance estimators (eg, SD, 95% CI, SE, interquartile range [IQR]), and methods, tariff, or algorithm applied (eg, EQ-5D using UK tariffs).

Assessment of methodological quality

We applied the 11-item Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Systematic Reviews and Research Syntheses.[17] After initial calibration, 1 author (J.B.) applied this checklist, and a second author validated the responses (C.R.C.). Disagreements were solved by consensus or, if necessary, with the help of a third author (E.N.D.G.). We coded responses and calculated the percentage of positive responses (positive responses over the total evaluated items). We classified the quality of each SR according to the scale proposed by Jadczak et al: low (0%-33%), medium (34%-66%), and high quality (≥67%).[21]

Assessment of overlapping

We measured the extent of overlapping primary studies by extracting references of primary studies from each SR, using a citation matrix, and calculating the "corrected covered area."[22] Overlap was classified as slight (0%-5%), moderate (6%-10%), high (11%-15%), or very high (>15%).[22]

We identified overlapping data and selected 1 observation per sample of patients for analysis. When the same observation was reported in different SRs, we selected the 1 with complete data (ie, country, tariff, and algorithm). When data were complementary, we merged the findings into 1 observation. In case of multiple reporting (ie, results obtained using different tariffs or algorithms), we selected the most frequently used among the selected SRs. Finally, we reviewed the individual studies for incongruencies among SRs (ie, different values, methods, or the number of patients for the same primary study).

Data Analysis

Content analysis

To reflect the natural disease progression and the treatment management challenges patients encounter in real-life scenarios, we performed a content analysis using the categories from the World Health Organization protocols,[23] which included the following: (1) T2DM: the T2DM diagnosis; we included T2DM (without other specifications) and T2DM without complications.; (2) acute complications: acute events because of uncontrolled glucose levels, including hyperglycemia and hypoglycemia with different severity levels; (3) microvascular complications: lesions from longstanding uncontrolled glucose levels, including retinopathy, nephropathy, neuropathy, and diabetic foot complications; (4) macrovascular complications: lesions in large vessels, including coronary heart disease, cerebrovascular disease, and peripheral vascular disease; (5) comorbidities: occurrence of nondiabetic related comorbidities; and (6) management of diabetes: strategies to prevent or manage diabetes complications. For the latter, management strategies were categorized into 3 (1) level

of glucose control, (2) modality of care, including usual care and nonpharmacological strategies, and (3) pharmacologic treatment and other interventions. One author proposed an initial codification (J.B.), and a group of 3 additional authors validated it (E.N.D.G., P.A.C., and A.V.M.). Disagreements were solved with the help of experts in the field.

Descriptive statistics

We described utility and disutility estimates per outcome using the range, mean, and SD (in the case of normally distributed samples) or median and IQR. Results from DCEs studies were narratively summarized.

Meta-analysis

We performed a meta-analysis of utility and disutility values for outcomes with >1 observation. Values obtained through different methods for 1 sample were analyzed as separate observations. The unit of analysis was an observation of a sample measuring outcome utility or disutility values with a specific method. Following published methodological guidance,[24,25] we

Figure 1. Flow diagram of the screening process.

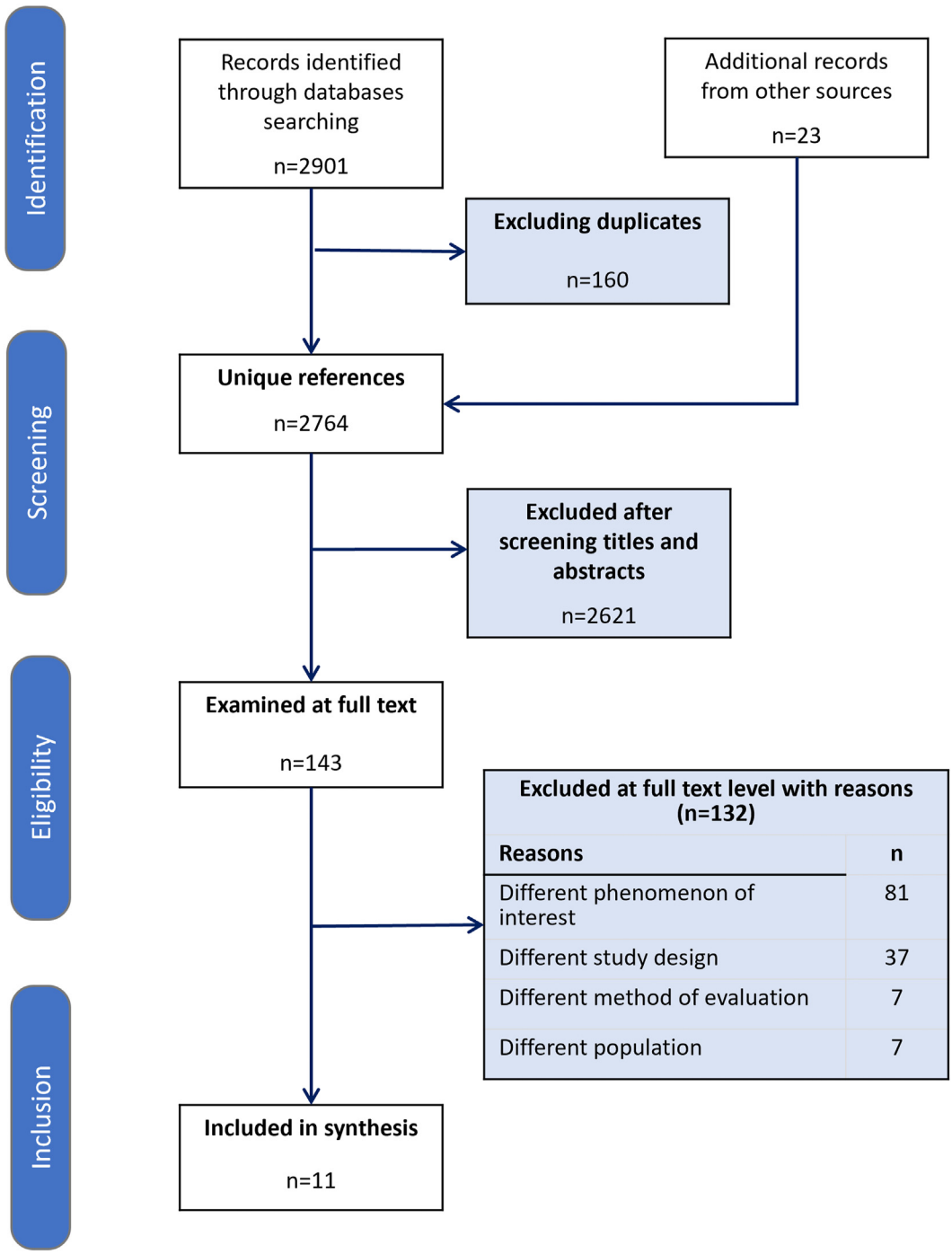

Table 1. General characteristics

SR author year, country	N included studies and design	N participants and characteristics	Outcomes*	Methods to obtain utilities (tariffs)	Quality assessment of included studies
Alleman et al, 2015[34] UK	30. Cohort and cross-sectional.	1,438. Patients with T2DM with diabetic polyneuropathy. One multicountry (Europe) and 1 from UK.	• Diabetic peripheral neuropathic pain.	• EQ-5D	Not evaluated.
Beaudet et al, 2014[35] UK	21. Cohort and cross-sectional.	22 724. Most were patients with T2DM. Most from Europe, some from Asia, America, and Australia.	• T2DM without complications. • Major hypoglycemia event, minor hypoglycemia event. • HF, ischemic heart disease, MI, PVD, stroke. • Diabetic retinopathy, visual acuity (severe affection), blindness, cataract, diabetic kidney disease, end-stage renal disease (hemodialysis, peritoneal dialysis), diabetic peripheral neuropathy, amputation, lower extremity disease: foot ulcers, moderate macular edema. • Excess BMI, overweight, obesity.	• EQ-5D (UK, US, The Netherlands, South Korea) • TTO	Not evaluated.
Brennan et al, 2015[36] UK	24. Economic evaluations with utility estimates and utility elicitation studies.	35,145. Patients with T2DM experiencing a stroke or MI. Most from Europe, others from America, Australia, and a few from Asia or Africa.	• T2DM. • HF, ischemic heart disease, MI (<1 year, 2-5 years, >5 years), CVD NS, stroke (<1 year, 2-5 years, >5 years), TIA, cerebrovascular disorder NS. • One complication NS. • Comorbidities NS.	• 15D (Finland) • EQ-5D (UK, The Netherlands, Sweden, Germany, Korea, US) • HUI-2 • HUI-3 (Canada) • QWB-SA (US) • SF-12, SF-12-MEPS • SF-36v1, SF-6D (Finland) • TTO	Three criteria: 9 of 16 utility studies were high study quality. Four did not control for confounding, and 3 were not representative of patients with T2DM.
Janssen et al, 2011[26] The Netherlands	59. Cross-sectional, experimental, longitudinal.	48,563. General population including patients with T2DM. Patients with 1 or more complications/comorbidities. Some included T1DM and T2DM or not explicitly excluded patients with T1DM. Most were from Europe, others from America, and 1 from Asia.	• T2DM, T2DM without complications. • Daytime hypoglycemia, hyperglycemia, hypoglycemia, hypoglycemic symptom severity, and night-time hypoglycemia. • HF, ischemic heart disease, MI, PVD, CVD NS, stroke cerebrovascular disorder NS, macrovascular complications NS. • Diabetic retinopathy, visual acuity affection, blindness, ophthalmologic complications NS, diabetic kidney disease, end-stage renal disease, diabetic peripheral neuropathic pain (mild, moderate, severe), diabetic peripheral neuropathy, foot ulcers, primary healed foot ulcer, neuropathy and PVD microvascular NS, amputation. • One complication, 2 or more complications, N of complications NS. • Hypertension, excess BMI, overweight, obesity, extreme obesity, depression, comorbidities NS. • Glucose control, diet and exercise, intensive blood glucose control, less intensive self-monitoring, more intensive self-monitoring, usual care, treatment: oral, with or without insulin, coronary artery bypass graft.	• EQ-5D (Japan, UK, US)	Not evaluated.

continued on next page

Table 1. Continued

SR author year, country	N included studies and design	N participants and characteristics	Outcomes*	Methods to obtain utilities (tariffs)	Quality assessment of included studies
Kennedy-Martin et al, 2015[37] UK	11. Cross-sectional.	22 477. Patients with T1DM or T2DM. Most from USA, others from Canada, UK, Finland, Iran, Japan and Thailand.	• T2DM, T2DM without complications • Diabetic kidney disease, end-stage renal disease (dialysis, transplant, no dialysis) • Microalbuminuria • Diet and exercise	• 15D • EQ-5D (Japan, UK, US) • QWB, QWB-SA • TTO	Not evaluated.
Lung et al, 2011[27] Australia	45. Studies reporting QALYs.	53 282. Patients with T1DM or T2DM. Male (%) 52.7% (range 25%-99%). Weighted average age: 62.6 y (range 37-77 y). (Country not reported).	• T2DM, T2DM without complications (< 5 years or ≥5 years). • MI, stroke (major, mild). • Amputation (major, mild), blindness, diabetic peripheral neuropathy. • Diabetic retinopathy, end-stage renal disease, foot ulcers. • Usual care, intensive blood glucose control.	• EQ-5D • HUI-3 • SF-6D • SG • TTO	Not evaluated.
Poku et al, 2013[38] UK	17. Studies of utility values.	1209. Patients with diabetic retinopathy. Female (%): 48%-58%. Mean age: 62.2 (SD 11.8) to 63.5 (SD 12.5). From USA; UK, and Canada.	• Blindness, diabetic retinopathy, visual acuity (mild, moderate, or severe affection).	• EQ-5D • HUI-3 • TTO	Two criteria: 1 study, 100% response rate. In the other 2, dropouts and response rates were unclear or missing.
Polinski et al, 2013[39] USA	10. DCEs.	378. One study included patients' perspectives: 227 patients (83%) with T2DM and 134 (49%) insulin users from Canada.	• Hypoglycemic episodes. • Weight gain. • Glycemic control.	• Willingness to pay	9-point checklist 3/9, due to lack of assessment or control for potential confounders.
Toroski et al, 2019[40] Iran	17. DCEs.	11 741. 16/17 studies included patients' perspectives. Most were from Europe, others from USA, Brazil, South Africa, and Canada.	• Hypoglycemic episodes. • Weight gain. • Glycemic control.	• Willingness to pay • Preference weights	AXIS They did not identify a high risk for bias.
von Arx and Kjær, 2014[42] Denmark	14. DCEs and contingent valuation.	19 087. 50% only patients with T2DM, the remaining recruited T1DM orT2DM. Most were from Europe, North America, and Australia.	• Glycemic control.	• Willingness to pay	10-item checklist: DCEs, 5 obtained 10/10, 1 9/10, 3 8/10, 3 7/10, and 1 5/10.
Zhou et al, 2018[41] China	38.Cross-sectional.	34 342. T2DM. Age: mean 50.7 (SD 17.31) to 68.3 (SD 13.3) Male (%): 33 to 56.1%. From China, Taiwan, and Hong Kong.	• T2DM, T2DM without complications. • PVD. • Obesity, overweight.	• EQ-5D (China, Japan, UK)	11-item checklist: scores ranged from 4/11 to 8/11 points.

NS complications were not included in metanalysis.
AXIS indicates Appraisal tool for Cross-Sectional Studies; BMI, body mass index; CVD, cardiovascular disease; DCE, discrete-choice experiment; HF, heart failure; HUI, Health Utilities Index; MEPS, Medical Expenditure Panel Survey; MI, myocardial infarction; NS, not specified; PVD, peripheral vascular disease; QALY, quality of life measure; QWB-SA, Quality of Well-Being Scale Self-Administered; SF-6D, Short Form-6-Dimension; SG, standard gamble; SR, systematic review; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; TIA, transient ischemic attack; TTO, time trade-off; UK, United Kingdom; US, United States; USA, United States of America.
*Outcomes labels after content analysis, presented grouped by categories.

considered a meta-analysis as an opportunity (1) to update and enhance the 2 most recent meta-analyses,[26,27] (2) to gain precision, including new studies per outcome, and (3) to apply a different metanalysis method compared with previous SRs. We transformed reported SDs and 95% CIs into SEs, by applying the conventional formula.[28] In case variance estimates were missing, we imputed these values with the mean of reported estimates for the same outcome.[28,29] We applied a random-effects model, assuming that studies estimate different, yet related effects.[30-32]

Heterogeneity

We expressed heterogeneity with the I^2-statistic, which can be quantified as low, moderate, and high, with upper limits of 25%, 50%, and 75% for I^2-statistic, respectively. For outcomes with 10 observations or more, we estimated the 95% prediction intervals to evaluate the potential impact of including a new similar study in the meta-analysis.[28,33] We used STATA software V.17 the syntaxis applied is available in Appendix Table 2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2023.07.003.

Results

Selection of SRs

The screening process is summarized in a flow diagram (Fig. 1). We initially identified 2901 references; and excluded 160 duplicates and 2615 references after screening the titles and abstracts. We reviewed 143 full texts and excluded 132 full texts (Appendix Table 3 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2023.07.003). We finally included 11 SRs, including a total of 152 studies.

General Characteristics

The main characteristics of included SRs are reported in Table 1.[26,27,34-42] All were published from 2011 and onward. Five were conducted in United Kingdom,[34-38] with the others being from Australia,[27] China,[41] Denmark,[42] The Netherlands,[26] Iran,[40] and United States.[39] The number of included studies ranged from 11[37] to 59,[26] with a range of participants from 378[39] to 53 282.[27] Most SRs (n = 8 of 11; 73%) included studies with variable designs (cross-sectional, cohort, experimental, and longitudinal). Three SRs included DCEs,[39,40,42] and 1 included economic evaluations.[36] Most SRs (n = 7 of 11; 64%) included a mixed population, with some studies focusing only on patients with T2DM, and others also included patients with T1DM. Three SRs included patients with T2DM only.[34,36,41] Six SRs included studies from worldwide, 5 with the majority of studies conducted in Europe,[26,34-36,40,42] and 1 with more studies from United States.[37] Two SRs included studies from 1 country only, Canada[39] and China.[41]

The most frequent method to estimate utility values was the EuroQoL (EQ-5D) (n = 8 of 11; 72%). Four SRs included, in addition to EQ-5D, the 15-dimensional self-administered questionnaire, HUI-3, HUI-2, SF-36 Health Survey, Quality of Well-Being Scale Self-Administered, SG, or TTO.[27,36-38] Finally, 3 SRs reported preference measures as the willingness to pay.[39,40,42] Only 2 SRs conducted a meta-analysis,[26,27] whereas the rest summarized findings narratively.

Assessment of Quality and Overlapping

According to the JBI Critical Appraisal Checklist and thresholds, most SRs were considered high quality, and only 1 was medium quality[34] (Table 2[26,27,34-42]). Six SRs (n = 6 of 11; 54%) assessed the quality of included studies[36,38-42]; each one applied different criteria or tools with variable quality results. We observe a slight overlap between the included SRs (2.35%) (Appendix Figs. 1 and 2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2023.07.003). Higher values typically emerge in more specific questions or when a limited number of study designs are included. Because we formulated a broad search strategy, a small overlap is coherent.

Data Set Development

After content analysis, we merged 271 different descriptions of outcomes (labels) into 70 outcomes and grouped them into 6 categories. We developed 2 data sets: (1) data set for descriptive statistics, including only 1 value per sample selecting the most frequent method across SRs, and (2) data set was for metanalysis, including all measures of a sample obtained with different methods, excluding no specific outcomes (eg, complications not specified). This data set included 427 observations from 119 primary studies. Original labels, tariffs reported, and data set for metanalysis are available online (Database_T2DM_values_2023.xlsx).

Utility and Disutility Values

Descriptive statistics are reported in Table 3, and Supplemental Material (Appendix Tables 4 and 5 and Appendix Figs. 3 and 4 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2023.07.003). By categories, the number of primary studies reporting utilities, ranged from 2 for acute complications to 86 for T2DM. Microvascular complications obtained the lowest median utility (median 0.61; IQR 0.460-0.735), and management of diabetes, the highest (mean 0.764; SD 0.094). The number of primary studies reporting disutilities ranged from 1 for management of diabetes to 17 for macrovascular complications. Macrovascular complications showed the highest median disutility (median −0.070; IQR −0.1217 to −0.37) and comorbidities, the lowest (median −0.032; IQR −0.0695 to −0.006). From here on, outcomes will be signaled in italic.

By outcomes, the lowest mean utility was for severe diabetic peripheral neuropathic pain (mean 0.225; SD 0.025), and the highest, for T2DM without complications (mean 0.793; SD 0.011). For disutilities, the range was between microalbuminuria (mean −0.003) and amputation (mean −0.205; SD 0.071). Utility and disutility mean values per outcome and, when possible, their pooled values are reported in Table 4.

T2DM

Utilities for T2DM were obtained from indirect (EQ-5D, SF-6D, HUI-3) and direct methods (SG, TTO). The most frequent was EQ-5D, pooled value of 0.768 (95% CI 0.754-0.783; I^2: 99.1%). Utilities for T2DM without complications were obtained from EQ-5D, SF-6D, and Quality of Well-Being Scale Self-Administered. The pooled value with EQ-5D was 0.799 (95% CI 0.781-0.81; I^2: 97.5%) (Appendix Figs. 5 and 6 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2023.07.003). The disutility for T2DM comparing female with male patients was −0.038, 1 observation. Eleven observations reported values for T2DM, according to age and disease duration, showing an increment of disutility per every 10 years age increment or according to the years with the diagnosis (Appendix Table 6 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2023.07.003).

Acute Complications

We obtained utility or disutility values for 10 acute events, all derived from EQ-5D. Hypoglycemia was reported with different severity, utilities decreased with increment of severity. The utility for *night-time hypoglycemia* was lower than the *daytime event* and the disutility for *major hypoglycemia* was 3 times the reduction of

Table 2. Critical appraisal of systematic reviews.

JBI checklist		Alleman et al[34]	Beaudet et al[35]	Brennan et al[36]	Janssen et al[26]	Kennedy-Martin et al[37]	Lung et al[27]	Poku et al[38]	Polinski et al[39]	Toroski 2019[40]	von Arx and Kjær[42]	Zhou et al[41]
1	Is the review question clearly and explicitly stated?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2	Were the inclusion criteria appropriate for the review question?	Yes	Yes	Yes	U	Yes	Yes	Yes	Yes	Yes	Yes	U
3	Was the search strategy appropriate?	U	Yes	Yes	Yes	Yes	Yes	Yes	Yes	U	Yes	Yes
4	Were the sources and resources used to search for studies adequate?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5	Were the criteria for appraising studies appropriate?	No	No	Yes	No	No	No	Yes	Yes	U	U	Yes
6	Was critical appraisal conducted by 2 or more reviewers independently?	No	No	U	No	No	No	Yes	Yes	Yes	U	U
7	Were there methods to minimize errors in data extraction?	U	U	Yes	Yes	Yes	U	Yes	Yes	U	U	Yes
8	Were the methods used to combine studies appropriate?	Yes	Yes	Yes	Yes	Yes	Yes	U	Yes	Yes	Yes	Yes
9	Was the likelihood of publication bias assessed?	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
10	Were recommendations for policy and/or practice supported by the reported data?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
11	Were the specific directives for new research appropriate?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	U
Overall		6/10	7/10	9/10	7/10	8/10	7/10	9/10	10/10	7/10	7/10	7/10

Green, positive appraisal; yellow, the response is unclear; red, negative appraisal; gray, not applicable.
JBI indicates Joanna Briggs Institute; NA, not applicable; U, unclear.

minor hypoglycemia, −0.159 (SD 0.11) and −0.045 (SD 0.028), respectively. In DCE studies, *avoiding hypoglycemia* willingness to pay varied from US$ 45/month to US$ 104/month; with higher values for *night-time events* (US$ 72-94)[39,40,42] and *one less major hypoglycemic event per year* (US$ 80-104).[40]

Macrovascular Complications

We obtained utilities or disutilities for 10 macrovascular complications. Most obtained from EQ-5D. We pooled utility or disutility values for *heart failure, ischemic heart disease, myocardial infarction, peripheral vascular disease, stroke*, and *transient ischemic attack* (Appendix Figs. 7 and 8 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2023.07.003). The lowest pooled estimates (from EQ-5D) were for *stroke* with 0.652 (95% CI 0.570-0.734; I^2: 96.5%), followed by *ischemic heart disease*, 0.659 (95% CI 0.475-0.843; I^2: 99.6%); *myocardial infarction*, 0.756 (95% CI 0.692-0.821; I^2: 90.5%), and *transient ischemic attack*, 0.785 (95% CI 0.716-0.854; I^2: 70.2%). The largest disutility was for *stroke*. Some observations for *myocardial infarction* or *stroke* considered the time after the event. If it was 5 years after the event, the disutility was reduced in two-thirds of the first year for *myocardial infarction* and a half for *stroke* (Appendix Table 6 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2023.07.003).

Microvascular Complications

We obtained utility or disutility values for 28 microvascular complications, we pooled 15 outcomes. Most were from EQ-5D; the second most frequent was TTO. Utility values (from EQ-5D)

Table 3. Descriptive statistics of utility and disutility values per outcomes category

T2DM outcomes categories	Measure	N studies	N observations	N participants*	Utility /disutility values mean/ median	SD/IQR	Min	Max
T2DM	Utilities	86	149	131 653	0.759	0.081	0.530	0.940
	Disutilities	1	2	1257	−0.0026	0.005	−0.038	−0.0163
Glycemic Complications	Utilities	2	8	410	0.689	0.083	0.540	0.800
	Disutilities	3	6	3689	−0.102	0.096	−0.270	−0.014
Macrovascular Complications	Utilities	13	41	33 924	0.719†	0.662 to 0.7655†	0.310	0.840
	Disutilities	17	47	56 214	−0.070†	−0.1217 to −0.37†	−0.590	0.067
Microvascular Complications	Utilities	31	100	21 811	0.610†	0.460 to 0.735†	0.200	0.91
	Disutilities	12	29	27 089	−0.0978	0.081	−0.28	−0.003
Comorbidities	Utilities	5	8	18 281	0.693	0.174	0.400	0.880
	Disutilities	7	8	10 549	−0.032†	−0.0695 to −0.006†	−0.202	−0.002
Diabetes Management	Utilities	11	28	6699	0.764	0.094	0.570	0.880
	Disutilities	1	1	NR	NA	NA	−0.049	−0.049

IQR indicates interquartile range (p25 to p75); Max, maximum value; Min, minimum value; NA, nonapplicable; NR, nonreported; T2DM, type 2 diabetes mellitus.
*Sum of the population when data was available.
†Variables without a normal distribution, values presented here are the median and IQR.

ranged from 0.225 (95% CI 0.176-0.274, I^2: 71.1%) for *severe diabetic peripheral neuropathic pain* to 0.830 (95% CI 0.819-0.841, 1 observation) for *end-stage renal disease with a transplant.* Utilities for *blindness* were 0.380 (95% CI 0.380-0.380; I^2: 0.0%) with TTO, and 0.640 (95% CI 0.576-0.704; I^2: 42.1%) from EQ-5D. The highest disutilities (from EQ-5D), were reported for *end-stage renal disease* and *amputation,* −0.228 (95% CI −0.385 to −0.070; I^2: 99.9%) and −0.205 (95% CI −0.344 to −0.066; I^2: 77%), respectively. *Microalbuminuria* showed the lowest disutility: −0.003 (95% CI −0.046 to 0.040, 1 observation), derived from 15-dimensional self-administered questionnaire.

Comorbidities

We identified utility or disutility values for 6 comorbidities. We pooled values for *overweight, obesity,* and the *excess body mass index per unit above 25.* Utilities ranged from 0.790 (95% CI 0.774-0.806) for *hypertension* to 0.400 (95% CI 0.363-0.437) for *extreme obesity.* Disutilities were reported for the *excess body mass index per unit above 25* and *depression*; the highest was for the latter (−0.202, 1 observation). Studies evaluating how patients value diabetes medication attributes found that patients with *obesity* value the reduction of body weight at least as important as the reduction of glycated hemoglobin, with some placing the highest value on losing weight.[40] DCEs studies reported a willingness to pay of $58 for 2 kg of weight gain per year instead of 6 or 10 kg.[39]

Management of Diabetes

We identified utility or disutility values for 14 outcomes, which were classified into 3 subgroups:

Level of Glucose Control

We found utility values for 4 levels of glucose control (*poor, fair, good,* and *excellent*) reported in 1 study conducted in Japan. There were no relevant differences between levels, with utilities higher than 0.8. DCEs studies reported that glycemic control was associated with a high willingness to pay, but it varied widely across studies ($28-$205/month). The lowest estimates were reported in studies including only insulin users, who reported a willingness to pay of $28 for having a blood glucose level of 9.4 mmol/liter 2 hours after a meal and $36 for having a blood glucose target within a range of 2 to 6 days a week.[39,42] Decreasing blood glucose and glycated hemoglobin levels (when increased) were the most important expected attributes of diabetes medications.[40]

Modality of Care

We identified utility values for *diet and exercise, self-monitoring, intensive glucose control with 2 modalities, less and more intensive glucose control,* and *usual care.* All reported at least 1 observation obtained from EQ-5D. The highest utility was for *diet and exercise* with 0.801 (95% CI 0.744-0.858, I^2: 92.3%), and the lowest was for *usual care,* 0.691 (95% CI 0.603-0.779, I^2: 99.2%).

Pharmacologic Treatment and Other Interventions

We identified values for 4 pharmacological agents and 1 procedure (*coronary artery bypass graft*). The highest utility was *noninsulin injectable treatment* with 0.850 (95% CI 0.825-0.875, 1 observation), and the lowest, for *insulin only or combined* with 0.630 (95% CI 0.595-0.665, 1 observation). The pooled utility for *oral antidiabetic agents* was lower than utility for *only insulin*, with 0.756 (95% CI 0.663-0.849, I^2: 96.3%) vs 0.773 (95% CI 0.607-0.939, I^2: 98.5%), respectively. Disutilities for *only insulin* represented the double of *oral antidiabetic agents* (−0.049 vs −0.025, respectively).

Heterogeneity

The majority of pooled utilities (n = 27 of 42, 64.3%) and disutilities (n = 8 of 14, 57.1%) showed high heterogeneity ($I^2 \geq 75\%$). Prediction Intervals were estimated for 4 outcomes; of these, *T2DM* and *T2DM without complications* showed confidence intervals not crossing the 0 value (Appendix Table 7 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2023.07.003). There was a wide variability between values derived from different methods within and across outcomes.

Discussion

Main Findings

We obtained utility or disutility values for 70 outcomes of T2DM from 11 SRs and 1119 primary studies. Utility values were retrieved for 47 outcomes. By categories, microvascular

Table 4. Mean utility and disutility values by T2DM outcomes.

Categories and Outcomes	Method	Utility* Mean [95% CI] I^2	O	Method	Disutility* Mean [95% CI] I^2	O
1. T2DM						
T2DM	EQ-5D	0.768 [0.754-0.783] 99.1%	64			
	TTO	0.784 [0.721-0.847] 95.1%	5			
	SF-6D	0.754 [0.707-0.800] 99.3%	8			
	SG	0.600 [0.504-0.696]	1			
	HUI-3	0.695 [0.567-0.822] 99.4%	5			
T2DM (without complications)	EQ-5D	0.799 [0.781-0.81] 97.5%	39	QWB-SA	−0.038[1]	1
	SF-6D	0.780 [0.762-0.798]	1			
	QWB-SA	0.670 [0.633-0.707] 86.1%	2			
2. Acute complications						
Hypoglycemia	EQ-5D	0.730 [0.690-0.770]	1			
Hypoglycemia no symptoms	EQ-5D	0.800 [0.760-0.840]	1			
Hypoglycemia mild symptoms	EQ-5D	0.730 [0.690-0.770]	1			
Hypoglycemia severe symptoms	EQ-5D	0.700 [0.660-0.740]	1			
Hypoglycemia very severe symptoms	EQ-5D	0.540 [0.500-0.580]	1			
Daytime hypoglycemia	EQ-5D	0.680 [0.640-0.720]	1			
Night-time hypoglycemia	EQ-5D	0.600 [0.560-0.640]	1			
Hyperglycemia	EQ-5D	0.730 [0.690-0.770]	1			
Major hypoglycemia				EQ-5D	−0.159 (SD 0.11)	3
Minor hypoglycemia				EQ-5D	−0.045 (SD 0.028)	3
3. Macrovascular complications						
Heart failure	EQ-5D	0.720 [0.659-0.781]	1	EQ-5D	−0.090 [−0.146 to −0.035] 73.6%	4
	QWB-SA	0.453 [0.392-0.514]	1	QWB-SA	−0.052 [−0.074 to −0.030]	1
Ischemic heart disease	EQ-5D	0.659 [0.475-0.843] 99.6%	3	EQ-5D	−0.048 [−0.065 to −0.032] 58.2%	8
	SF-6D	0.735 [0.708-0.762]	1	SF-6D	−0.027 [−0.059 to 0.005]	1
	HUI-3	0.630 [0.603-0.657]	1	HUI-3	−0.153 [−0.296 to −0.010] 97.5%	2
	15D	0.783 [0.756-0.810]	1	HUI-2	−0.077 [−0.109 to −0.045]	1
				15D	−0.036 [−0.068 to −0.004]	1
Unstable angina	EQ-5D	0.740 [0.698-0.782]	1			
Myocardial infarction	EQ-5D	0.756 [0.692-0.821] 90.5%	4	EQ-5D	−0.077 [−0.106 to −0.048] 84.6%	10
	SF-6D	0.765 [0.748-0.783] 0.0%	2	SF-6D	−0.019 [−0.077 to 0.039]	1
	HUI-3	0.770 [0.741-0.799]	1	SF-12-MEPS	−0.040 [−0.098 to 0.018]	1
	SF-12-MEPS	0.692 [0.664-0.720]	1	SF-36v1	−0.017 [−0.075 to 0.041]	1
	SF-36v1	0.665 [0.654-0.676]	1			
Peripheral vascular disease (PVD)	EQ-5D	0.800	1	EQ-5D	−0.084 [−0.124 to −0.045] 41.7%	4
Stroke	EQ-5D	0.652 [0.570-0.734] 96.5%	7	EQ-5D	−0.116 [−0.143 to −0.09] 87.1%	13
	SF-6D	0.729 [0.697-0.762] 51.5%	2	SF-6D	−0.043 [−0.079 to −0.007] 0.0%	2
	HUI-3	0.790 [0.731-0.849]	1	HUI-3	−0.370 [−0.801 to 0.061] 99.3%	2
	15D	0.754 [0.717-0.791]	1	HUI-2	−0.370 [−0.421 to −0.319]	1
	SF-12-MEPS	0.659 [0.622-0.696]	1	15D	−0.056 [−0.107 to −0.005]	1
	SF-36v1	0.648 [0.632-0.664]	1	SF-12-MEPS	−0.077 [−0.128 to −0.026]	1
	SF-12	0.762 [0.740-0.784]	1	SF-36v1	−0.034 [−0.085 to 0.017]	1
				SF-12	−0.042 [−0.093 to 0.009]	1
Mild stroke	TTO	0.700 [0.677-0.723]	1			
Major stroke	TTO	0.310 [0.287-0.333]	1			

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Table 4. Continued

Categories and Outcomes	Method	Utility* Mean [95% CI] I^2	O	Method	Disutility* Mean [95% CI] I^2	O
Stroke with residual				EQ-5D QWB-SA	−0.094 [−0.145 to −0.043] −0.072 [−0.103 to −0.041]	1 1
Transient ischemic attack	EQ-5D	0.785 [0.716-0.854] 70.2%	2	EQ-5D	−0.052 [−0.076 to −0.029] 47.8%	3
4. Microvascular complications						
Diabetic retinopathy	EQ-5D TTO	0.704 [0.585-0.823] 97.4% 0.703 [0.536-0.871] 99.2%	5 3	EQ-5D	−0.012	1
Diabetic retinopathy (moderate)				EQ-5D	−0.04	1
Diabetic retinopathy (severe)				EQ-5D	−0.07	1
Visual acuity mild affection	EQ-5D TTO	0.750 [0.711-0.789] 0.0% 0.869 [0.839-0.898] 0.0%	2 2			
Visual acuity moderate affection	EQ-5D TTO	0.584 [0.482-0.685] 29.0% 0.782 [0.758-0.805] 14.8%	4 4	EQ-5D	−0.110 [−0.188 to −0.032] 87.0%	2
Visual acuity severe affection	EQ-5D TTO	0.450 [0.185-0.714] 0.0% 0.663 [0.546-0.780] 74.4%	2 2	EQ-5D	−0.150 [−0.228 to −0.072]	1
Blindness	EQ-5D SF-6D TTO	0.640 [0.576-0.704] 42.1% 0.769 [0.740-0.798] 0.380 [0.380-0.380] 0.0%	4 1 5	EQ-5D	−0.057 [−0.135 to 0.021]	1
Cataract				EQ-5D	−0.016 [−0.031 to −0.001]	1
Moderate macular edema				EQ-5D	−0.0400	1
Diabetic kidney disease	EQ-5D QWB-SA TTO	0.715 [0.659-0.771] 46.5% 0.509 [0.409-0.609] 0.640 [0.540-0.740]	6 1 1	EQ-5D QWB-SA	−0.047 [−0.090 to −0.004] −0.011 [−0.054 to 0.032]	1 1
End-stage renal disease	EQ-5D TTO SG	0.470 [0.407-0.532] 99.2% 0.350 [0.326-0.374] 0.400 [0.310-0.490]	8 1 1	EQ-5D	−0.228 [−0.385 to −0.070] 99.9%	4
End-stage renal disease - dialysis	EQ-5D QWB-SA	0.627 [0.571-0.684] 98.8% 0.477 [0.334-0.620] 99.7%	3 2	EQ-5D QWB-SA	−0.060 [−0.138 to 0.018] −0.078 [−0.156 to 0.000]	1 1
End-stage renal disease - no dialysis	EQ-5D	0.760 [0.749-0.771]	1			
End-stage renal disease - transplant	EQ-5D TTO QWB-SA	0.830 [0.819-0.841] 0.820 [0.809-0.831] 0.620 [0.609-0.631]	1 1 1			
Macroalbuminuria				15D	−0.036 [−0.079 to 0.007]	1
Microalbuminuria	EQ-5D	0.800 [0.700-0.900]		15D	−0.003 [−0.046 to 0.040]	1
Proteinuria				EQ-5D	−0.048 [−0.091 to −0.005]	1
Diabetic peripheral neuropathic pain	EQ-5D	0.459 [0.424-0.495] 63.9%	5			
Diabetic peripheral neuropathic pain (mild)	EQ-5D	0.610 [0.571-0.649] 54.9%	2			
Diabetic peripheral neuropathic pain (moderate)	EQ-5D	0.475 [0.387-0.563] 91.1%	2			
Diabetic peripheral neuropathic pain (severe)	EQ-5D	0.225 [0.176-0.274] 71.1%	3			
Diabetic peripheral neuropathy	EQ-5D SG	0.690 [0.581-0.800] 98.1% 0.870 [0.815-0.925]	5 1	EQ-5D	−0.121 [−0.191 to −0.051] 63.5%	4
Lower extremity disease: Foot ulcers	EQ-5D TTO SG	0.521 [0.401-0.641] 97.8% 0.660 [0.635-0.685] 0.693 [0.556-0.830] 85.8%	7 1 2	EQ-5D	−0.127[−0.238 to −0.017] 81.9%	3
Primary healed foot ulcer	EQ−5D	0.600	1			

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Table 4. Continued

Categories and Outcomes	Method	Utility* Mean [95% CI] I^2	O	Method	Disutility* Mean [95% CI] I^2	O
Lower extremity disease: Neuropathy and PVD				EQ-5D	−0.085 [−0.171 to 0.001]	1
Amputation	EQ-5D	0.490 [0.207-0.773] 91.8%	3	EQ-5D	−0.205 [−0.344 to −0.066] 77%	3
	SF-6D	0.730 [0.689-0.771]	1			
	TTO	0.500 [0.402-0.598] 95.8%	2			
Major amputation	EQ-5D	0.310 [0.228-0.392]	1			
	SG	0.610 [0.531-0.689]	1			
Minor amputation	EQ-5D	0.610 [0.528-0.692]	1			
	SG	0.740 [0.675-0.805]	1			
5. Comorbidities						
Hypertension	EQ-5D	0.790 [0.774-0.806]	1			
Excess BMI per unit above 25				EQ-5D	0.006 [0.008-0.004] 0.0%	3
Overweight	EQ-5D	0.777 [0.603-0.951] 98.5%	3			
Obesity	EQ-5D	0.673 [0.502-0.845] 98.4%	3			
Extreme obesity	EQ-5D	0.400 [0.363-0.437]	1			
Depression				EQ-5D	−0.202	1
6. Diabetes management						
Level of glucose control						
Glucose control (excellent)	EQ-5D (Japan)	0.870 [0.820-0.920]	1			
Glucose control (good)	EQ-5D (Japan)	0.880 [0.840-0.920]	1			
Glucose control (fair)	EQ-5D (Japan)	0.860 [0.820-0.900]	1			
Glucose control (poor)	EQ-5D (Japan)	0.850 [0.800-0.900]	1			
Modality of care						
Diet and exercise	EQ-5D	0.801 [0.744-0.858] 92.3%	4			
	QWB-SA	0.689 [0.649-0.729]	1			
Intensive blood glucose control	EQ-5D	0.800 [0.771-0.829]	1			
	TTO	0.705 [0.578-0.832] 97.3%	2			
Less intensive self-monitoring	EQ-5D	0.760 [0.757-0.763]	1			
More intensive self-monitoring	EQ-5D	0.730 [0.727-0.733]	1			
Usual care	EQ-5D	0.691 [0.603-0.779] 99.2%	4			
	TTO	0.760 [0.740-0.780]	1			
Pharmacological treatment and other interventions						
Oral antidiabetic Agent	EQ-5D	0.756 [0.663-0.849] 96.3%	4	EQ-5D	−0.025	1
Insulin only or combined	EQ-5D	0.630 [0.595-0.665]	1			
Only insulin	EQ-5D	0.773 [0.607-0.939] 98.5%	3	EQ-5D	−0.049	1
Non-insulin injectable treatment	EQ-5D	0.850 [0.825-0.875]	1			
Coronary artery bypass graft	EQ-5D	0.790 [0.759-0.821]	1			

Note: 1 female: apply 0.038 decrement over male.
15D indicates 15-dimensional self-administered questionnaire; BMI, body mass index; HUI-3, Health Utilities Index-3; MEPS, Medical Expenditure Panel Survey; O, observations; QWB-SA, Quality of Well-Being Scale Self-Administered; SF-6D, Short Form-6-Dimension; SG, standard gamble; T2DM, type 2 diabetes mellitus; TTO, time trade-off.
*Pooled values for studies reporting >1 observation, SD. This was reported in cases no data was available to estimate Standard Error).

complications showed the lowest median utility and management of diabetes, the highest. The outcomes with the lowest utility values were: *hypoglycemia with very severe symptoms* (acute complications), stroke (macrovascular complications), *diabetic peripheral neuropathic severe pain (*microvascular complications*), extreme obesity (*comorbidities*), and insulin only or combined* (management of diabetes*).* On the other extreme, *good, excellent glucose control* and *noninsulin injectable treatment* showed higher mean values compared with utility for *T2DM without complications* (0.799 [95% CI 0.781-0.81; I^2: 97.5%]). Disutility values were reported for 31 outcomes, the highest disutilities were for *amputation*, *depression*, *major hypoglycemia event*, *stroke*, and *only insulin*. The majority of pooled estimates showed high heterogeneity ($I^2 \geq 75\%$).

Our Findings in the Context of Previous Research

To our knowledge, this is the first overview of SRs of studies exploring patients' preferences based on quantitative studies of utility estimates for outcomes of T2DM. Two included SRs also performed a meta-analysis for some outcomes. Lung et al[27] applied a random-effect meta-analysis (without restricting by type of method). Janssen et al applied a fixed-methods model, limiting the analysis to studies using EQ-5D with United Kingdom tariffs.[26] We identified a more significant number of observations for some outcomes, resulting in more precise estimates. The development of SRs of studies reporting utility or disutility estimates is an evolving research field in chronic conditions. For example, 1 SR for Chronic Obstructive Pulmonary Disease has also conducted a meta-analysis and applied the GRADE approach to assess the certainty of evidence.[43]

Strengths and Limitations

Our study has several strengths. Our broad, inclusive criteria allowed the inclusion of SRs using any method and country.[25] Half of the SRs included participants from all over the world; however, most studies were developed in high-income countries. Despite the high variability in data reporting, we identified and merged comparable outcomes using structured and detailed data extraction, data cleaning, and iterative content analysis to classify outcomes. We restricted analysis by type of method (or tool), providing comparable pooled values for most outcomes. We estimated prediction intervals for some outcomes to test the impact of additional observation results on heterogeneity. Similarly, to previous studies, we identified a high heterogeneity with reasons being difficult to explain.[25,32,44]

Our study also has limitations. Because we did not explore the role of other potential sources of heterogeneity, such as differences in study design or context, some caution should be warranted when interpreting results. Some SRs provided detailed and comprehensive reporting of a single measure; however, for our analysis, we selected the most frequently reported tariff, or algorithm across SRs. Finally, we did not evaluate the certainty of the evidence because there is still scant guidance on adapting GRADE methodology to overviews.[24]

Implications for Further Research

Our findings represent the perspective of patients regarding the importance of T2DM complications and outcomes of diabetes treatment. They characterize how patients value outcomes, a key criterion for developing trustworthy recommendations, for example, when using the GRADE evidence to decision framework.[7] This evidence may inform the development of decision support tools, such as decision aids, by considering the outcomes with high impact (eg, *neuropathic pain*). Our findings may be applied in cost-utility analyses. We also identified some outcomes with still scarce data, including acute complications (eg, *hyperglycemia)* and management of diabetes (eg, *type of glucose control*).

Our methods may complement guidance to develop overviews of SRs of health utility estimates. Because of the uncertainty about which type of method reflects better patients' preferences, we suggest considering the different methods to estimate utilities. It is necessary to develop guidelines for reporting outcomes in SRs; we found high variability in labels reporting for outcomes across SRs, making content analysis very challenging. Despite labels being fully detailed in primary studies, some SRs modified them. There is also room for improvement in guidance for quality assessment. None of the SRs evaluated the certainty of the evidence, with only half assessing the methodological quality of primary studies; however, with different tools. Tools for this purpose include the one proposed by GRADE.[8] We found some items of the JBI Critical Appraisal Checklist too broad, and the thresholds applied[21] did not discriminate well SRs quality. Thus, it is preferable to report the results narratively. Finally, a qualitative research synthesis, including qualitative and mixed methods, could be insightful for evaluating this topic.[18]

Conclusions

We provide standardized, reliable utility values (or associated disutilities), reflecting how patients with T2DM value T2DM, microvascular and macrovascular complications, related comorbidities, and treatments. These results could support healthcare decision making when making clinical recommendations, designing decision-support tools and developing interventions and economic analysis.

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