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Measurement and valuation of health and capability well-being outcomes in adults with coeliac disease

PhD thesis

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List of Abbreviations

AD – Anxiety/Depression (EQ-5D-5L)

AQoL – Assessment of Quality of Life

ANOVA – Analysis of Variance

CD – Coeliac Disease

CFI – Comparative Fit Index

CFA – Confirmatory Factor Analysis

CI – Confidence Interval

CO – Cognition (bolt-on)

DI – Dining (bolt-on)

DWLS – Diagonally Weighted Least Squares

EQ VAS – EQ Visual Analogue Scale

EQ-HWB – EQ Health and Wellbeing

EUR – Euro (currency)

GFD – Gluten-Free Diet

GI – Gastrointestinal problems (bolt-on)

GSRS – Gastrointestinal Symptom Rating Scale

HTA – Health Technology Assessment

HRQoL – Health-Related Quality of Life

HUF – Hungarian Forint

H′ – Shannon index (absolute informativity)

ICECAP-A – ICEpop CAPability measure for Adults

ICECAP-O – ICEpop CAPability measure for Older people

IQR – Interquartile Range

J′ – Shannon evenness index (relative informativity)

LSS – Level Sum Score

MO – Mobility (EQ-5D-5L)

NICE – National Institute for Health and Care Excellence

OLS – Ordinary Least Squares

PCA – Principal Component Analysis

PD – Pain/Discomfort (EQ-5D-5L)

PROM – Patient-Reported Outcome Measure

PROMIS-29+2 – Patient-Reported Outcomes Measurement Information System 29+2

QALY – Quality-Adjusted Life Year

QoL – Quality of Life

RE – Relative Efficiency

RMSEA – Root Mean Square Error of Approximation

SC – Self-Care (EQ-5D-5L)

SD – Standard Deviation

SE – Standard Error

SF-36 – 36-item Short Form

SF-6D – Short Form 6 Dimensions

SL – Sleep (bolt-on)

SPSS – Stat. Package for Social Science

SWLS – Satisfaction With Life Scale

TI – Tiredness (bolt-on)

TTO – Time Trade-Off

UA – Usual Activities (EQ-5D-5L)

VAS – Visual Analogue Scale

WEMWBS – Warwick-Edinburgh Mental Well-Being Scale

WHO – World Health Organization

WHO-5 – WHO-5 Well-Being Index

WiX – Well-being instrument

WOOP – Well-being of Older People

WTP – Willingness To Pay

1. Introduction

1.1. Quality of life and health-related quality of life

A clear conceptualisation of quality of life (QoL) and health-related quality of life (HRQoL) is essential for comprehensively capturing individuals' lived experiences, perceptions, expectations and personal values within healthcare settings.

QoL is a broad and multidimensional concept, often without a universal definition [1, 2]. The World Health Organization (WHO) defines QoL as *"an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns"* [3]. This definition emphasises that QoL is a subjective and context-dependent construct. Individuals living under similar conditions may evaluate their quality of life differently, as their judgements are shaped by cultural background, personal values, expectations and life goals. This highlights the inherently subjective nature of QoL: it must be understood from the individual's own perspective [4].

Defining HRQoL has been challenging as multiple interpretations appear in the literature [5]. One definition conceptualises HRQoL as reflecting individuals' functioning in daily life and their perceived well-being across physical, mental, and social domains of health [6]. Another approach conceptualises HRQoL in relation to QoL, as QoL covers all aspects of an individual's life, while HRQoL represents the subset specifically related to health [7]. A further definition conceptualises HRQoL as those aspects of quality of life that are directly affected by health, disease, or treatment [8]. Finally, an additional perspective shifts the focus to the value of health states. In this approach, HRQoL denotes the values (utilities) assigned to different health conditions [9].

HRQoL can be understood more clearly by maintaining a distinction between health status and overall QoL. In this view, HRQoL may either represent the utility or value assigned to specific health states, or it may describe the empirically measured impact of health on a person's broader QoL [5]. Such conceptual distinctions help minimise overlap between related constructs [10, 11].

1.2. Utility

Assessing the value of different health states requires consideration of preferences and their quantification through utility measures. Only a subset of HRQoL instruments allows

the assignment of health utility values to different health states (i.e. preference-accompanied measures). Utilities reflect how preferred certain health outcomes are on a scale anchored on ‘full health’ (1) and ‘being dead’ (0) [12]. Health states can sometimes be perceived as worse than dead in which case they are assigned negative utility values. A range of methods exist to estimate utilities. These can be categorised into direct and indirect approaches. Direct elicitation techniques, such as the Standard Gamble and Time Trade-Off (TTO), require individuals to make explicit judgements about the value of different health states [12, 13]. In contrast, indirect methods rely on preference-accompanied HRQoL instruments, for example, the EQ-5D, the Short Form 6 Dimensions (SF-6D), the Assessment of Quality of Life (AQoL), and the Patient-Reported Outcomes Measurement Information System 29+2 (PROMIS-29+2), where individuals describe their HRQoL and responses are converted into utility values using societal value sets [14, 15].

1.3. Quality-adjusted life year

Utilities play a fundamental role in health economic evaluations and health technology assessment, as they allow health outcomes to be expressed on a common, preference-based scale. Their application is essential in reimbursement evaluations of pharmaceuticals, medical devices and public health interventions, where decision-makers must determine whether the health benefits gained justify the financial investment required. Utilities are integral to the calculation of quality-adjusted life years (QALYs), the standard metric used in cost-utility analyses [14, 16, 17].

The QALY consolidates both quantity (life years) and quality (utility) into one standardised metric, enabling comparisons across diverse healthcare interventions and supporting consistent, evidence-based priority setting [18]. QALY shows the time spent in a certain health state, for example, four years spent in a health state with a utility of 0.2 equals 0.8 QALYs [14, 18].

Although QALYs are widely used in health economic evaluations, their application is not without concerns [19-21]. Ethically, QALYs have been criticised for potentially favouring younger or non-disabled individuals, which raises questions about fairness in resource allocation. Methodological issues also persist, including the subjective nature of HRQoL assessment, differences between utility elicitation methods, and the impact of

discounting on long-term outcomes. Additionally, QALYs do not distinguish whether health improvements are distributed across many individuals or concentrated within a single patient [22].

1.4. HRQoL measures

As modern healthcare increasingly prioritises patient experience and outcomes, HRQoL measurement has become essential in both clinical research and health technology assessment (HTA) [23, 24].

HRQoL is commonly assessed using patient-reported outcome measures (PROMs), standardised questionnaires that capture health status directly from the patient's perspective. These tools can be categorized into two major types: generic and disease-specific measures [25]. Generic HRQoL instruments, such as the SF-36 and EQ-5D, allow comparisons across different diseases and populations. Their broad scope supports use in economic evaluations and resource allocation decisions, particularly when utilities are derived to QALYs [26]. However, they may lack sensitivity to specific symptoms, treatment effects, or disease burdens relevant to distinct patient groups [25].

Disease-specific HRQoL measures have been developed to focus on symptoms, functional limitations, and psychosocial impacts that are relevant to a particular conditions, thereby capturing clinically meaningful changes [27]. In HTA, disease-specific preference-accompanied instruments may play an important role in some specific populations, where generic measures may lack content validity [28, 29]. Nonetheless, the number of such validated tools remains limited, and challenges persist in comparing outcomes across different health conditions [24, 26]. Furthermore, in countries where generic measures are recommended by national HTA guidelines and bodies as the reference case, these represent a deviation [30].

1.5. Well-being concept and measures

Well-being is a broad, multidimensional concept that goes beyond clinical indicators to capture individuals' subjective experiences and overall life evaluation [31]. While HRQoL focuses on the impact of disease and treatment on health status, well-being encompasses emotional, social, and functional aspects that contribute to living a fulfilling life. As healthcare systems shift toward person-centred outcomes, well-being

measurement has become increasingly important for understanding the holistic effects of chronic illnesses [32, 33].

Well-being may be measured using instruments such as the WHO-5 Well-Being Index, the Warwick-Edinburgh Mental Well-Being Scale (WEMWBS), the Satisfaction with Life Scale (SWLS), the EQ Health and Wellbeing (EQ-HWB), the 10-item Well-being instrument (WiX), or the Well-being of Older People (WOOP) [34-39]. These instruments are valuable predictors of future mental and physical health outcomes and can detect unmet needs not visible through HRQoL alone.

In addition to subjective well-being metrics, a complementary perspective is offered by the capability approach, that distinguishes achieved states ("functionings") from the opportunities to attain them ("capabilities") [40, 41]. This perspective emphasises people's freedom and possibility [42]. As such, it has particular relevance in economic evaluations aiming to reflect the full impact of health and interventions [43]. This perspective is particularly relevant in chronic illness, where patients may adapt to limitations, report acceptable HRQoL scores, yet still experience restricted opportunities, autonomy, and social participation. Instruments such as the ICEpop CAPability measure for Adults (ICECAP-A) and ICEpop CAPability measure for Older people (ICECAP-O) have been developed to assess capability well-being in economic evaluations, offering a broader assessment of how health systems support individuals to lead meaningful lives [44-46].

Reflecting this, several national HTA guidelines have acknowledged their relevance. In the UK, when the National Institute for Health and Care Excellence (NICE) expanded its remit to include social care in 2013, it recommended the use of capability-based measures, such as the ICECAP instruments for economic evaluations in this sector [47]. Similarly, the Dutch National Health Care Institute (Zorginstituut) advises including ICECAP and EQ-HWB alongside the EQ-5D in long-term care evaluations, recognising that important outcomes in these settings extend far beyond health status alone [48].

From a policy standpoint, well-being indicators are increasingly being incorporated alongside HRQoL in value-based healthcare frameworks [49-51]. While QALY-based outcomes facilitate comparability across conditions, they are not intended to capture components of well-being such as dignity, independence. Integrating subjective, capability-based, and health-specific outcomes provides a richer understanding of

treatment benefit and helps ensure resource allocation aligns with what matters most to patients and society [52-54].

1.6. HRQoL and well-being measures used in this thesis

The primary data collections presented in this thesis applied a set of outcome measures to capture both health-related and broader well-being aspects of coeliac disease. These included a generic preference-accompanied instrument (EQ-5D-5L), one disease-specific symptom measure (GSRS), two well-being measures (SWLS and ICECAP-A), two direct utility elicitation methods (TTO and VAS), and a contingent valuation method (WTP).

1.6.1. EQ-5D-5L

The EQ-5D-5L contains a descriptive component with five health dimensions and a separate visual analogue scale (EQ VAS) that captures current health status (‘today’) [55]. The descriptive system covers mobility (MO), self-care (SC), usual activities (UA), pain/discomfort (PD), and anxiety/depression (AD) dimensions, each answered on a 5-point severity scale, ranging from ‘no problems’ to ‘extreme problems/unable to’. Combining the five dimensions yields 5^5=3125 distinct health profiles; for example, a “11111” profile reflects no reported problems in any of the five dimensions, representing the best possible health state. The EQ-5D-5L can be scored using national value sets for the calculation of QALYs [56].

In addition to the descriptive system, the EQ VAS records respondents’ overall perception of their health on a vertical visual analogue scale. The scale is anchored at 0 (‘the worst health you can imagine’) and 100 (‘the best health you can imagine’). This provides a quantitative measure of self-rated health that is complementary to the descriptive system, offering sensitivity to changes in health status that may not be fully captured by the five dimensions [57].

Among different generic preference-accompanied instruments, the EQ-5D has become the most widely applied measure [58]. It has shown good validity and responsiveness in a wide range of acute and chronic health conditions [59]. Moreover, it is recommended by HTA guidelines in more than 20 countries, including Hungary [30, 60, 61]. While the EQ-5D is valid and reliable in the majority of populations, it may perform suboptimal in some specific health conditions, given its limitations in content validity in certain HRQoL areas [62].

1.6.2. EQ-5D-5L bolt-ons

A “bolt-on” refers to an additional dimension added to the EQ-5D-5L descriptive system that covers a dimension not captured by the core five dimensions (e.g., fatigue, cognition, sleep) [63, 64]. Bolt-ons typically use the same five-level severity structure and refer to current health status (‘today’). The inclusion of bolt-ons can expand the measurement coverage of the instrument and enhance its responsiveness to disease-specific changes in health status. Bolt-ons may increase the accuracy of utility estimates, leading to more reliable cost-effectiveness evaluations [64-69].

1.6.3. Gastrointestinal Symptom Rating Scale

Gastrointestinal Symptom Rating Scale (GSRS) was originally developed to assess common gastrointestinal symptoms in peptic ulcer disease and irritable bowel syndrome. It has since been applied extensively in clinical trials and real-world research involving CD [70-73]. The GSRS consists of 15 items, organised into five symptom domains: reflux (two items), abdominal pain (three items), indigestion (four items), diarrhoea (three items), and constipation (three items). The recall period is the past 7 days. Each item is rated on a seven-point Likert scale, ranging from ‘no discomfort at all’ (1) to ‘very severe discomfort’ (7). Item scores are summed to form a total score from 15 to 105, where lower values indicate fewer or less severe gastrointestinal symptoms [70].

1.6.4. Satisfaction with Life Scale

The Satisfaction with Life Scale (SWLS) was used to assess the patients’ subjective well-being. This measure consists of 5 statements rated on a 7-point likert scale [36]. Summed scores range from 5 to 35, with higher totals indicating greater overall life satisfaction, where respondents evaluate ‘in general’ rather than over a specific short-term recall period. Developed for use in general and clinical populations, the SWLS has demonstrated strong reliability and validity to life changes [36, 74-76]. It is particularly useful in conditions where health status may not fully capture the lived impact of chronic illness, and where psychosocial adaptation plays a major role in patient outcomes [77-80].

1.6.5. ICECAP-A

The ICECAP-A assesses current (‘at the moment’) capability well-being in adults aged 18-64 years across five attributes: stability (feeling settled and secure), attachment (having love, friendship and support), autonomy (being independent), achievement (being

able to achieve and progress), and enjoyment (experiencing enjoyment and pleasure) [44]. These attributes reflect key aspects of a person’s life: stability relates to continuity in areas such as friendships, employment, and living situation; attachment highlights the value of emotional support and social bonds; autonomy reflects the importance of independence and self-sufficiency; achievement captures personal growth and goal attainment; and enjoyment represents the ability to find joy in daily life. The measure asks respondents to assess themselves with a recall period of ‘at the moment.’ Each attribute has four response levels, ranging from ‘no capability’ (level 1) to ‘full capability’ (level 4) resulting in 4^5 = 1,024 possible response combinations. Index values were derived using the Hungarian value set, which assigned a value to each response profile between 0 (no capability) and 1 (full capability) [81]. The Hungarian version of the ICECAP-A has previously undergone validation in general population and patient samples, supporting its reliability and validity [82-84].

1.6.6. Time trade-off

The time trade-off (TTO) method elicits utility values for imperfect health states by asking patients to make a trade-off between quality and length of life [12]. We opted to use a 10-year time frame, as this is the most commonly used duration in valuation studies in Hungary and beyond [56, 85-92]. Patients were asked to imagine living in their current health or in a hypothetical CD-related health state for the next 10 years, followed by death. Then they had to indicate how many life years they would give up in order to regain full health. We used the top-down titration; thus, respondents were offered a predefined list with responses ranging from 10 years to 0 years, with the smallest tradable amount of time being 6 months. TTO utilities were computed using the following formula:

$$Utility = 1 - \frac{Patient's\ answer}{10\ years}$$

For example, in case a patient indicated to give up three years, the corresponding utility value was calculated as U=1-(3/10)=0.7. There was no worse-than-dead task in this study, therefore utilities ranged from 0 (being dead) to 1 (full health).

1.6.7. Visual Analogue Scale

The Visual Analogue Scale (VAS) is a simple and widely used method for capturing patients’ subjective assessment of overall health. It can be administered either horizontally or vertically, typically as a line anchored at the endpoints by contrasting

statements representing the worst imaginable health state (=0) and the best imaginable health state (=100). Respondents indicate their perceived health by marking a point along the line, which is then quantified by measuring the distance from the lower anchor. Its flexibility makes it suitable for use in both clinical practice and research settings, including trials and observational studies across a wide range of health conditions [93].

1.6.8. Willingness to pay

Willingness to pay (WTP) measures the maximum amount of money an individual would be willing to pay to be free from their own symptoms or those described in the vignettes in our study [94]. Monthly WTP values were recorded in a closed question format with an open-ended ‘other’ response option. Sixteen predefined monthly amounts (in HUF) were offered to patients based on a previous survey: none; 500; 1,000; 2,000; 4,000; 6,000; 8,000; 10,000; 15,000; 20,000; 25,000; 30,000; 45,000; 60,000; 80,000 and 100,000 [95]. WTP data can support economic evaluation by providing monetary estimates of patient-perceived benefit, which are particularly valuable in areas where improvements to daily life and subjective well-being are key outcomes. From a policy perspective, incorporating WTP into evaluation frameworks offers a broader understanding of societal value and can inform more patient-centred resource allocation decisions [96].

1.6.9. Vignette-based measurement

Vignette-based health state testing is a methodology used to evaluate the impact of health states by presenting respondents with structured hypothetical scenarios. These vignettes typically describe symptoms, functional limitations, and psychosocial consequences in a standardised manner, enabling respondents to evaluate health conditions that they may not have personally experienced [91].

In valuation studies, vignettes are often paired with preference elicitation techniques such as TTO, or WTP assessments. Vignette-based preference elicitation is particularly useful when existing generic instruments are insensitive to disease-specific impacts or when deriving utilities directly from patients is impractical - for example, when assessing rare symptom patterns or pre-diagnosis experiences [97].

1.7. Psychometric properties of HRQoL and well-being measures

For HRQoL and well-being instruments to be useful in clinical and social care settings and health and social policy, they must demonstrate strong measurement performance. Psychometric testing examines whether a tool can capture patient experiences accurately, consistently, and in a way that reflects meaningful changes in health or well-being over time. To determine whether a measure can be trusted to inform practice and policy, three core measurement properties are typically assessed: responsiveness, reliability, and validity [98, 99].

Responsiveness is a critical requirement for instruments used to evaluate treatment outcomes and disease progression. It reflects the ability of an instrument to detect clinically important differences in health or well-being over time, whether those changes reflect improvement or deterioration [100].

Reliability concerns measurement precision. It determines whether similar results can be expected when there is no meaningful change in the respondent's actual health or well-being. Reliability can be expressed through test-retest reliability or by evaluating the extent to which items within a domain work together statistically. However, this latter approach is relevant only for scales constructed to measure a single underlying concept [101].

Validity is ultimately concerned with whether an HRQoL or well-being measure captures the concept that it claims to assess [100]. Evidence for validity can come from several sources. Content validity evaluates whether the items represent the full scope of relevant patient experiences, ensuring clarity and relevance for the population being studied [101]. Construct validity considers how well results align with theoretical expectations, including the ability to distinguish between groups of differing health or well-being, or demonstrate relationships with other validated outcomes. Criterion validity, although commonly referenced in measurement theory, cannot usually be applied to generic HRQoL instruments because there is no universally accepted gold standard against which to compare them [102].

While longitudinal designs are required to explore stability and sensitivity to change, a substantial proportion of validity testing can be undertaken within a cross-sectional design framework [102, 103].

1.8. Coeliac disease (CD)

1.8.1. Definition, pathogenesis and epidemiology

Coeliac disease (CD) is an immune-mediated systemic disorder triggered by the ingestion of gluten in genetically susceptible individuals, most commonly those carrying HLA-DQ2 or HLA-DQ8 genotypes. Following gluten ingestion, incompletely digested gliadin peptides reach the small intestinal mucosa, where tissue transglutaminase (tTG) deamidates them. This triggers a pathogenic immune response. The resulting mucosal damage is characterised by varying degrees of villous atrophy, crypt hyperplasia, and chronic inflammation, ultimately impairing nutrient absorption [104-106]. Population prevalence ranging between 0.7% and 1.4% with considerable geographic variation and evidence of a rising incidence over recent decades. This increase is attributed not only to improved diagnostic awareness and testing but also to genuine epidemiological growth, underscoring CD as an expanding public-health concern [107, 108]. CD can develop across the entire lifespan and is approximately 1.5 times more common in females than males [107, 109, 110].

1.8.2. Clinical spectrum, extraintestinal manifestations and comorbidities

CD presents with a broad clinical spectrum ranging from classical gastrointestinal symptoms to predominantly extraintestinal or even asymptomatic forms. Gastrointestinal manifestations include chronic diarrhoea, abdominal pain, bloating, constipation and symptoms of malabsorption, such as weight loss, iron-deficiency anaemia, vitamin deficiencies and osteoporosis [111]. Extraintestinal manifestations are increasingly recognised and play a critical role in disease burden and HRQoL impairment. These include neurological symptoms (headache, peripheral neuropathy, ataxia), dermatological manifestations (dermatitis herpetiformis), reproductive disorders, hepatic abnormalities and a range of psychiatric and neurocognitive conditions. CD is associated with an increased prevalence of depression, anxiety disorders, attention-deficit/hyperactivity disorder and eating disorders [112, 113]. Furthermore, CD frequently coexists with other autoimmune diseases, such as type 1 diabetes mellitus, autoimmune thyroid disease and autoimmune liver disorders, further increasing disease complexity and long-term management demands [114].

1.8.3. Dietary treatment and long-term management

At present, strict and life-long adherence to a gluten-free diet (GFD) is the only available and effective treatment for CD [115]. According to international standards, foods labelled as gluten-free must contain less than 20 parts per million (ppm) of gluten. Patients must navigate complex dietary rules, including differentiation between certified gluten-free products (e.g. crossed-grain symbol) and naturally gluten-free foods, while also considering the nutritional quality of gluten-free processed foods, which may be higher in fat, sugar and salt and lower in fibre and micronutrients [116]. Long-term management includes regular clinical follow-up, dietary counselling, monitoring of serological markers, assessment of micronutrient status and screening for complications. These requirements represent an ongoing burden for patients and healthcare systems as well [117, 118].

1.8.4. Impact of CD and GFD on HRQoL and well-being

Maintaining a GFD places a substantial burden on patients due to the limited availability, high cost and often inferior quality of gluten-free products, as well as lifestyle-related difficulties such as restricted social eating and limited support from peers [119-126]. Although adherence to the GFD has consistently been associated with substantial improvements in HRQoL [127-130], evidence also indicates that these gains may be incomplete. A recent meta-analysis reported that HRQoL, while improved, does not fully normalise in individuals with CD, even when the diet is strictly followed [131]. Patients frequently report persistent fatigue, cognitive difficulties, anxiety and feelings of social exclusion, highlighting that CD continues to adversely affect day-to-day functioning and psychological well-being even after treatment initiation [132-134].

1.9. Gaps in evidence

1.9.1. Scarcity of utility and WTP data

EQ-5D has been the most frequently used instrument to derive health utilities in CD, although studies reported similar or even higher utilities in patients than those observed in the general population [129, 130, 135], underscoring important limitations of the instrument. Another key methodological limitation of prior research is that the vast majority of individuals with CD were already adhering to a GFD at the time of evaluation. Accordingly, utility values for the pre-treatment phase could only be elicited

retrospectively, an approach inherently vulnerable to recall bias [12, 130, 135-138]. As a consequence, no reliable utility estimates are available for CD before treatment. Furthermore, no existing studies have systematically investigated the relationship between varying degrees of dietary adherence and health utility outcomes.

As vignettes are hypothetical, they enable to elicit preferences for any health state. Preferences for the vignettes may be measured in several ways; for example, people may trade off life years (TTO) or risk of death (standard gamble) to improve health. Although TTO is the most widely used method to directly obtaining health utilities [139]; however, no studies to date have applied this approach among patients with CD. Preferences can also be assessed through contingent valuation, in which respondents indicate the amount they would be willing to pay to improve their health. To date, two studies have employed this method in CD. One study measured WTP for CD screening in parents of children diagnosed with CD in Sweden, and another one surveyed adult patients with CD in Switzerland [140, 141]. However, no vignette-based WTP studies have been carried out in CD to date.

1.9.2. Need for broadening the content of EQ-5D-5L in CD

In gastrointestinal conditions, the EQ-5D pain/discomfort dimension may not fully reflect non-pain forms of physical discomfort. Although "discomfort" is intended to capture a broader set of sensations, respondents often interpret this dimension primarily as pain, which can lead to underrepresentation of gastrointestinal-related burden [142]. Consequently, in conditions where gastrointestinal symptoms are central, such as CD, there is a potential to improve the instrument's validity and sensitivity. EQ-5D may overestimate HRQoL in patients with CD, which is supported by three earlier EQ-5D studies from the UK, Poland and Slovenia reporting better HRQoL in CD patients after diagnosis compared to the general population [129, 130, 135]. One possible solution to enhance the coverage of the EQ-5D is the addition of 'bolt-ons' to the instrument. So far, several bolt-ons have been developed for the EQ-5D; for example, a skin irritation and self-confidence bolt-on for patients with chronic skin diseases [65, 143, 144], a vision bolt-on for patients with vision problems, such as cataract [69, 145], and a respiratory bolt-on for patients with asthma and chronic obstructive pulmonary disease [146]. The added value of these bolt-ons varies, and in some cases the impact on utility estimates is

minimal [147]. For instance, introducing a sleep bolt-on to the EQ-5D-3L produced only minimal changes in utility values [66].

1.9.3. Limited evidence on well-being in CD

Generic HRQoL instruments may overlook important aspects of living with CD that extend beyond symptoms and physical functioning. Even when patients' clinical status is stable, many individuals experience food-related anxiety, restrictions around eating in social settings, and practical limitations affecting travel or work-related occasions, all of which can meaningfully shape day-to-day well-being [132-134]. To date, relatively few studies have examined the well-being of patients with CD, most of which rely on the Psychological General Well-being index [148-151]. Furthermore, the psychometric properties of existing well-being measures (e.g. ICECAP-A) have not been thoroughly examined in the context of CD.

2. Objectives

This thesis includes three original studies, each addressing a specific gap in the HRQoL and well-being measurement in patients with CD.

2.1. Preference elicitation study

Economic evaluations require reliable utility estimates that reflect the true burden of disease. Existing evidence on utilities in CD is limited and largely based on EQ-5D [129, 130, 135-137, 152]. However, EQ-5D-derived utilities may overestimate HRQoL, while no reliable time TTO utilities have been reported for CD health states. Similarly, WTP studies are scarce [140, 141], and no vignette-based WTP evidence is available in this patient population. Therefore, this study aims are the following:

- Generate VAS scores and TTO utility values for self-experienced and hypothetical CD health states.
- Elicit WTP estimates through contingent valuation to assess the monetary value patients assign to symptom relief and dietary control.
- Identify demographic and clinical predictors of VAS scores, TTO utilities and WTP values.

2.2. EQ-5D-5L bolt-on study

The EQ-5D-5L's five dimensions may not fully reflect the symptom profile of CD, particularly with respect to gastrointestinal and psychosocial problems. Bolt-on dimensions have been proposed as a means to enhance the descriptive richness of the EQ-5D-5L by including additional dimensions relevant to CD. To address existing validity limitations, this study aims are the following:

- Evaluate measurement properties, including distributional characteristics, ceiling, convergent and known-group validity of five EQ-5D-5L bolt-ons in adult patients with CD.

2.3. ICECAP-A psychometric testing study

The ICECAP-A was developed to assess capability well-being and may therefore provide a broader evaluation of the consequences of CD. However, its measurement properties in this population have not yet been tested. Thus, this study aims to:

- Examine the psychometric performance of the ICECAP-A in adult CD patients, including distributional properties, convergent validity with HRQoL and subjective well-being measures (SWLS), and known-group validity.
- Compare ICECAP-A results with EQ-5D-5L to determine whether capability measurement provides added value to general HRQoL assessment.

3. Methods

This chapter draws upon three published articles of the candidate:

1. Angyal M Mercédesz, Lakatos Péter L, Jenei Balázs, Brodszky Valentin, Rencz Fanni: Health utilities and willingness to pay in adult patients with coeliac disease in Hungary. QUALITY OF LIFE RESEARCH 32: 9 pp. 2503-2516. (2023).
2. Angyal M Mercédesz, Janssen Mathieu F, Lakatos Péter L, Brodszky Valentin, Rencz Fanni: The added value of the cognition, dining, gastrointestinal problems, sleep and tiredness bolt-on dimensions to the EQ-5D-5L in patients with coeliac disease. EUROPEAN JOURNAL OF HEALTH ECONOMICS 26: 3 pp. 473-485. (2025)
3. Angyal M Mercédesz, Pangestu Stevanus, Lakatos Péter L, Brodszky Valentin, Rencz Fanni: Psychometric testing of the ICECAP-A in patients with coeliac disease: a comparative analysis with EQ-5D-5L. HEALTH AND QUALITY OF LIFE OUTCOMES 23: 1 Paper: 112, 11 p. (2025)

3.1. Study design and data collection

3.1.1. Cross-sectional survey design

All three studies included in this dissertation were based on the same cross-sectional survey of adult patients with CD in Hungary. Data collection took place between November 2020 and January 2021. Patients were recruited via the Hungarian Coeliac Society, regional patient organisations, and multiple social media platforms targeting individuals living with CD. Participation in the survey was voluntary, anonymous, and uncompensated. The questionnaire was hosted on the Qualtrics survey platform (Qualtrics, Provo, UT, USA), which allowed for a secure and user-friendly online data collection process.

Participants were required to meet the following inclusion criteria: (i) age 18 years or older, (ii) self-reported physician-confirmed diagnosis of CD, and (iii) provision of informed consent prior to participation. Exclusion criteria were the absence of a physician-confirmed diagnosis, incomplete questionnaires, or survey completion times shorter than eight minutes, as these were considered indicative of low-quality responses. All procedures involving human participants were conducted in accordance with the

ethical standards of the institutional and/or national research committee, as well as with the 1964 Declaration of Helsinki and its later amendments. Ethical approval was obtained from the Research Ethics Committee of the Corvinus University of Budapest (reference number: KRH/390/2020).

3.1.2. Questionnaire structure and data analyses

The questionnaire consisted of four parts. The first part included questions about CD-related clinical characteristics, including disease duration, comorbidities and adherence to GFD. This section was built on two earlier national surveys involving CD patients in Sweden and the UK [129, 130]. The second part consisted of different standardised questionnaires to assess symptoms, HRQoL and well-being. Respondents first completed the EQ-5D-5L descriptive system (including bolt-on dimensions) and the EQ VAS, followed by the ICECAP-A and the SWLS. Gastrointestinal symptoms were then assessed using the GSRS. In the third part of the survey, the patients were asked to assess their own health, followed by three hypothetical health-state vignettes, which appeared in a randomised order. *Both* current own health and the hypothetical health state vignettes were valued by two direct utility assessment methods, VAS and TTO and by contingent evaluation asking WTP. All HRQoL measures used in this thesis were administered in Hungarian. In the last part of the questionnaire, sociodemographic data, including age, gender, employment, place of residence, net household income and education, were collected. Data were analysed using Stata 14.0 (StataCorp. 2015, College Station, TX, USA), R 4.2.0 (R Core Team, 2022, Vienna, Austria), and IBM SPSS Statistics 28.0 and 29.0 (IBM Corp., 2022, Armonk, NY, USA). For all analyses, a $p<0.05$ was considered statistically significant.

3.2. Preference elicitation study

3.2.1. Outcome measures

Respondents initially rated their current health status, and subsequently evaluated three hypothetical health-state vignettes that were displayed in a randomized order. Time trade-off, willingness to pay and VAS methods were used to assess utilities and preferences.

The following three hypothetical health state vignettes developed for this study: (1) CD without GFD, (2) CD with loose adherence to GFD and (3) CD with strict adherence to GFD. The vignettes were presented from a second-person perspective (Table 1.). The

vignettes were primarily developed based on existing literature reviews [127, 131, 153-155]. A recently published model on concepts relevant when assessing health outcomes in CD summarizes the signs and symptoms as well as broader HRQoL aspects in CD based on 28 original studies and stakeholder interviews with clinical experts and payers [155]. The model incorporates both gastrointestinal and non-gastrointestinal signs and symptoms of the disease alongside the following six HRQoL aspects: daily activities (e.g. negative impact on career or work), relationships (e.g. family life), social/leisure (e.g. dining out), sleep, dietary burden of GFD (e.g. difficulty adhering to GFD) and psychological impacts (e.g. anxiety or depression). These HRQoL impacts overlap with those covered by the most widely used patient-reported outcome measures in CD. Considering the conceptual model and thorough review of the item content of CD-specific HRQoL measures and symptom scales the following six areas were selected to be included in the health state vignettes based on judgement of a patient, a gastroenterologist professor and two health economists experienced in utility assessment: diet, gastrointestinal symptoms, work/school, physical activities, sleep/fatigue, mood and social life (Table 1). Comprehensibility of the descriptions was tested in an interview with a CD patient.

Table 1. Coeliac disease hypothetical health state descriptions (vignettes) [156]

	Health state 'A' **CD without GFD**	Health state 'B' **CD with loose adherence to GFD**	Health state 'C' **CD with strict adherence to GFD**
Diet	You are not on a diet; you may eat all kinds of food you want. You do not have to check the ingredient lists of food products.	You are on a special diet, which you more or less follow, so you often cannot eat all kinds of food you want. You need to check the ingredient lists of food products.	You are on a special diet that you follow strictly, so you cannot eat all kinds of food you want. You need to check the ingredient lists of food products.
Gastro-intestinal symptoms	After meals, you often experience bloating, constipation or diarrhoea on a weekly basis. Bloating is often associated with abdominal pain or cramps, nausea or vomiting.	After some meals you may experience bloating, constipation or diarrhoea. Bloating is often associated with abdominal pain or constipation.	After meals, you do not experience bloating, constipation or diarrhoea. You hardly ever have abdominal pain or cramps.

Work/ school	Your health makes it difficult to carry out your duties at work or school properly, you often have to take time off work or miss school for medical appointments. At work/school you can eat with your peers in the canteen.	You are able to perform your work or school duties properly. You rarely have to take time off work or miss school for medical appointments. At work/school you cannot eat with your peers in the canteen.	Your condition does not prevent you from carrying out your duties at work or school. At work/school, you cannot eat with your peers in the canteen.
Physical activities	Your digestive complaints (bloating, diarrhoea, constipation, vomiting or abdominal pain) prevent you from exercising, doing chores or shopping. In general, you feel weak to perform physical activities.	In rare cases, your digestive complaints (bloating, diarrhoea, constipation, vomiting or abdominal pain) may prevent you from exercising, doing chores or shopping. You sometimes feel weak to perform physical activities.	You are not prevented from exercising, doing housework or shopping. You generally do not feel weak to perform physical activities.
Sleep/ fatigue	Your abdominal pain or cramps often prevent you from falling asleep. You are regularly tired and feeling low during the day, you find it difficult to concentrate and need more sleep at night.	You sometimes experience tiredness and feel low during the day, but you have no difficulty with concentration. At night, you can sleep as much as you need.	You are not tired or feel low during the day, and you do not have any difficulty with concentration. At night, you can sleep as much as you need.
Mood and social life	You experience mood swings, you are periodically depressed, and you experience less desire for the company of others. You are able eat with your peers at any social event.	Your mood is stable and you do not have depression. At social events, you are prevented from eating with your peers. You are often unable to eat at meetings because the café/restaurant cannot provide meals that suit your diet.	Your mood is stable and you do not have depression. At social events, you are prevented from eating with your peers, and you have to plan meals in advance. You are often unable to eat at meetings because the café/restaurant cannot provide meals that suit your diet.

The vignettes were constructed through literature review and expert consultation, focusing on domains most affected by CD (dietary restrictions, gastrointestinal symptoms, energy levels, sleep, mood, social participation). A pilot test with a CD patient ensured comprehensibility and face validity.

3.2.2. Analyses

Socio-demographic and clinical characteristics of the patients were analysed using descriptive statistics. The difference in GSRS scores between female and male patients was tested by Mann-Whitney *U* test. WTP responses were converted into a yearly value and then to euros, based on the European Central Bank's closing conversion rate for February 2021 (EUR 1= HUF 361.01). Nonsensical WTP responses (e.g. 'I cannot tell') were excluded from the data analysis. Descriptive statistics (mean, median, standard deviation and IQR, proportion of '0' and maximum responses) were computed for VAS, TTO and WTP values. The differences in VAS, TTO and WTP values across the patients' own health and the three hypothetical health states were tested by Friedman test. Predictors of VAS, TTO and WTP values were explored by using multivariate regression models (OLS for own health and random-intercept linear models for hypothetical health states). Insignificant variables were removed from the models by backward stepwise elimination. Before the regressions, a logarithmic transformation was applied to normalise the distribution of the WTP responses. Heteroscedasticity was evaluated by Breusch-Pagan test and corrected by using robust standard errors.

3.3. EQ-5D-5L bolt-on study

3.3.1. Development and selection of bolt-ons

In this study, we used both newly developed condition-specific bolt-ons and relevant existing bolt-ons for the EQ-5D-5L (bolt-on dimensions are copyright-protected, permission is required to reproduce them; they are available in Supplementary Material 1 of Angyal et al. (2025) [157]). The development and selection of bolt-ons were informed by a literature review on HRQoL in CD as well as relevant domains from existing relevant condition-specific measures, and expert input. The panel of experts comprised a CD patient, a gastroenterologist professor and two health economists experienced in utility assessment.

A conceptual model summarising the most important health outcomes in patients with CD has recently been published [155]. This conceptual model, based on an analysis of the item content of condition-specific measures and additional interviews with both CD clinical experts and payers, encompasses two large symptom groups (gastrointestinal and extra-intestinal) and six aspects of HRQoL. The most common gastrointestinal symptoms included in CD-specific measures are bloating, nausea, diarrhoea, abdominal pain/discomfort, loose stool and flatulence. The most common extra-intestinal symptoms in these instruments are low energy/fatigue, headaches, food cravings and slowness/difficulty thinking. The six HRQoL areas include daily activities (e.g. mobility, self-care, reduced concentration), psychological impact (e.g. anxiety, depression, stress, mental fatigue), relationships (e.g. stigmatization, family life), social or leisure (social activities, dining out at restaurants), sleep (e.g. insomnia), and treatment/dietary (e.g. bathroom usage, difficulty adhering to a GFD). While the five dimensions of the EQ-5D-5L seem to provide a good coverage of the main symptoms and HRQoL aspects of CD, there might be some important areas missed out, where the addition of bolt-ons could be particularly useful. Based on the frequency of the abovementioned symptoms and HRQoL impacts and discussions between members of the expert panel, the decision was taken to develop two new condition-specific bolt-on dimensions to more comprehensively reflect the psychosocial and physical burden of CD on HRQoL: dining (DI), which featured examples of ‘following a diet’ and ‘eating out’, and gastrointestinal problems (GI), listing the following examples in parentheses: diarrhoea, constipation, nausea, vomiting, heartburn, bloating and gases. Furthermore, we selected three existing bolt-ons that held relevance in the context of CD: cognition (CO), sleep (SL) and tiredness (TI) [158, 159], presented in Online Resource 1. The CO bolt-on was deemed especially relevant as CD patients can experience certain neurologic and psychiatric manifestations, including cerebellar ataxia, peripheral neuropathy, brainstem dysfunction, epilepsy, dementia, headache and depression [160-162]. A ‘social relationships’ bolt-on dimension was not included in the study as we considered that it would potentially overlap with some aspects of HRQoL covered by the DI bolt-on (eating out) as well as the usual activities EQ-5D-5L dimension.

Both bolt-on dimensions were framed the same manner as the EQ-5D-5L dimensions, featuring a short dimension title accompanied by a few examples in parentheses and the

same number of and severity-type response levels ranging from 'no problems' to 'extreme problems' [64]. When selecting the examples for the dimensions, we relied on both the language used in qualitative expert interviews in an earlier study and item wordings of commonly used condition-specific instruments [155]. The language and wording of the two bolt-on dimensions were finalized based on input gathered from a CD patient and subsequent discussions within the expert panel.

3.3.2. Analyses

We followed an established psychometric framework for bolt-on testing [64, 68, 147]. First, each individual bolt-on was tested separately, and subsequently, various combinations of bolt-ons were examined. Each bolt-on was tested separately, then combined incrementally based on performance. Descriptive analyses reported response distributions; ceiling was quantified at item and instrument level (11111 profiles with/without bolt-ons). Informativity was assessed using Shannon index (H′) and Shannon evenness (J′) [163]. We hypothesized that adding bolt-on(s) would lead to a reduction in the ceiling and an improvement in both the absolute and relative informativity.

Spearman's rank-order correlations (r_s) were used to test the associations between EQ-5D-5L dimensions, bolt-ons, GSRS domains and EQ VAS. Correlation coefficients were interpreted as very weak (<0.20), weak (0.20-0.39), moderate (0.40-0.59), strong (0.60-0.79) and very strong (≥0.80) [164]. We assumed that the GI bolt-on would demonstrate moderate or strong correlation with GSRS domains and total score as well as with the pain/discomfort EQ-5D-5L dimension. This latter hypothesis arises from the understanding that certain gastrointestinal symptoms are associated with at least some physical discomfort [142]. Further, we anticipated a moderate correlation between i) CO and TI with usual activities; ii) SL and TI with pain/discomfort; iii) CO, SL and TI with anxiety/depression [165-169]. Regarding the DI bolt-on, our hypothesis was that the bolt-on dimension would exhibit a (very) weak correlation with the five core EQ-5D-5L dimensions due to the conceptual distinction between them.

Known-group validity was tested via LSS (0–100) across self-rated health, GSRS tertiles, and presence of symptoms; relative efficiency (F-ratio) compared EQ-5D-5L+bolt-on(s) vs EQ-5D-5L, with 95% CIs from 3,000 bootstraps. Additional bolt-ons were retained only if they significantly improved F-ratios. Univariable and multivariable linear

regressions assessed explanatory power for EQ VAS and SWLS (unadjusted; adjusted for age, gender, GSRS). Bolt-ons were added incrementally and retained only if adjusted R^2 increased.

PCA (promax) and CFA (DWLS) explored dimensionality using EQ-5D-5L and its bolt-ons, GSRS domains, SWLS items. Factors followed Kaiser's criterion [170]. Factor loadings were interpreted based on the following reference values: ≤0.32 (unacceptable), 0.33-0.45 (poor), 0.45-0.54 (fair), 0.55-0.62 (good), 0.63-0.70 (very good) and ≥0.71 (excellent) [171]. CFA was used to test whether the data fit to our hypothesized measurement model. To address the ordinal nature of dimensions, we employed the diagonally weighted least squares (DWLS) estimator to compute factor loadings. Model fit was considered acceptable when the root mean square error of approximation (RMSEA) was less than 0.08 and the comparative fit index (CFI) exceeded 0.90 [172].

3.4. ICECAP-A psychometric testing study

3.4.1. Outcome measures

ICECAP-A were used as the primary outcome measure to assess capability well-being in individuals with CD. Psychometric properties assessed included distributional characteristics, convergent validity with the Gastrointestinal Symptom Rating Scale (GSRS) and Satisfaction with Life Scale (SWLS) and known-group validity.

3.4.2. Analyses

The applied analyses framework used in the present study have been used in previous ICECAP-A and ICECAP-O validation studies in general population and various patient samples [45, 83, 173]. Measurement properties of the ICECAP-A were assessed and compared with those of the EQ-5D-5L to evaluate overall instrument performance. The distributions of responses across the ICECAP-A attributes and EQ-5D-5L dimensions were presented as relative frequencies and visualized using stacked bar charts. Ceiling values were calculated at both the level of individual attributes (or dimensions) and the overall instrument. Floor and ceiling effects were considered present if more than 15% of respondents reported the lowest or highest ICECAP-A or EQ-5D-5L index value, respectively [102]. Index values for the ICECAP-A and EQ-5D-5L, and EQ VAS were visualized using histograms, and stratified by age group using line charts.

We assessed convergent validity to examine whether ICECAP-A attributes and index values aligned with similar constructs of other measures, and divergent validity to test whether they differed from unrelated ones. Correlations between ICECAP-A and EQ-5D-5L, EQ VAS, GSRS, and SWLS were assessed [164]. For attribute- or dimension-level correlations, Spearman's rank-order correlation (r_s) was used, while Pearson's correlation (r_P) was applied to index values or instrument-level scores. The absolute value of correlation coefficients were interpreted as follows: very weak (<0.20), weak (0.20–0.39), moderate (0.40–0.59), and strong (≥0.60) [164]. We hypothesized that the ICECAP-A stability attribute would show at least moderate correlation with the anxiety/depression dimension of the EQ-5D-5L, given their shared focus on emotional and psychological aspects [174]. Weak correlations were expected with the EQ-5D-5L mobility, self-care, and pain/discomfort dimensions, as these reflect physical health aspects less relevant to capability well-being. We anticipated moderate correlations between ICECAP-A autonomy and achievement and EQ-5D-5L usual activities dimension, given their mutual emphasis on daily functioning. Moreover, we expected moderate-to-strong correlations between ICECAP-A attributes and the SWLS [175, 176]. At the instrument level, we hypothesized that ICECAP-A index values would be moderately correlated with EQ-5D-5L index values based on previous studies [177-180].

Known-group validity was evaluated by testing whether the ICECAP-A could differentiate between groups based on characteristics expected to potentially affect capability well-being, including, comorbidities, symptoms, gastrointestinal problems (measured by GSRS), GFD duration, adherence to GFD, age, general health status, gender, education, place of residence, and employment. Differences in ICECAP-A scores between groups were assessed using t-tests (for two-group comparisons) and one-way ANOVA (for comparisons involving more than two groups). Effect sizes and their 95% confidence intervals were calculated: Cohen's d for two groups and eta-squared (η^2) for more than two groups. Effect sizes were interpreted as trivial ($d=0$–0.19, $\eta^2<0.01$), small ($d=0.20$–0.49, $\eta^2=0.01$–0.05), moderate ($d=0.50$–0.79, $\eta^2=0.06$–0.13), or large ($d\geq0.80$, $\eta^2\geq0.14$) [181-183]. For GSRS groups and general health status, we expected larger effect sizes for the EQ-5D-5L than for ICECAP-A given their health-specific focus. We expected both better health and capabilities in those following the GFD for a longer duration, and in patients adhering more strictly to the GFD [184]. We hypothesized that

with more comorbidities, as well as older patients and women would have significantly lower capability values [131, 185, 186], but we expected higher capability values among individuals with better self-perceived health, higher education levels, and employment status [44, 82]. Meanwhile, for sociodemographic factors such as education and employment status, we anticipated larger effect sizes for the ICECAP-A, reflecting its broader conceptualisation of well-being [177-180, 187].

4. Results

This chapter draws upon the findings of three published articles of the candidate:

1. Angyal M Mercédesz, Lakatos Péter L, Jenei Balázs, Brodszky Valentin, Rencz Fanni: Health utilities and willingness to pay in adult patients with coeliac disease in Hungary. QUALITY OF LIFE RESEARCH 32: 9 pp. 2503-2516. (2023).
2. Angyal M Mercédesz, Janssen Mathieu F, Lakatos Péter L, Brodszky Valentin, Rencz Fanni: The added value of the cognition, dining, gastrointestinal problems, sleep and tiredness bolt-on dimensions to the EQ-5D-5L in patients with coeliac disease. EUROPEAN JOURNAL OF HEALTH ECONOMICS 26: 3 pp. 473-485. (2025)
3. Angyal M Mercédesz, Pangestu Stevanus, Lakatos Péter L, Brodszky Valentin, Rencz Fanni: Psychometric testing of the ICECAP-A in patients with coeliac disease: a comparative analysis with EQ-5D-5L. HEALTH AND QUALITY OF LIFE OUTCOMES 23: 1 Paper: 112, 11 p. (2025)

During the data collection, a total number of 734 individuals were reached with our questionnaire. Out of 734 who opened the questionnaire, 455 (62.0%) finished it. Of these, 143 respondents were excluded based on the exclusion criteria (Figure 1). The final analytic sample consisted of 312 adult patients with CD. The majority of the patients were female (70.2%), and the average age at diagnosis was 27.1 years (SD=14.0) (Table 2.).

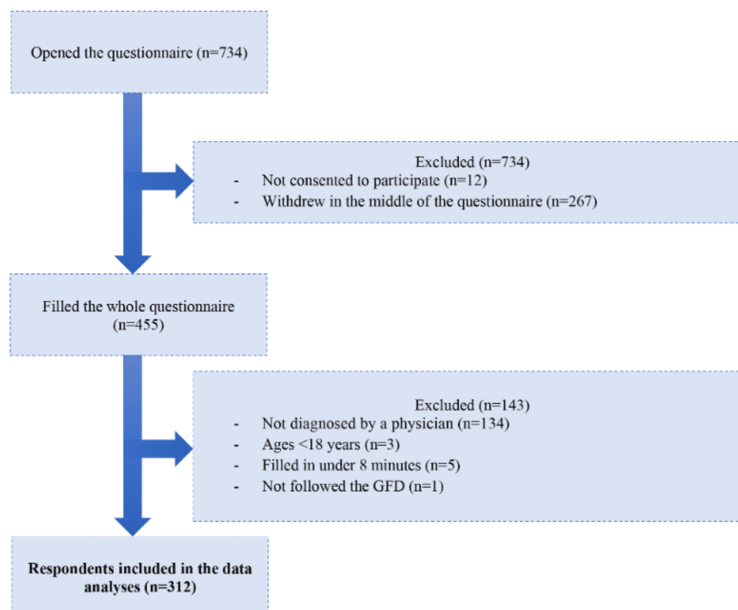

Figure 1. Study flow chart [156]

Table 2. Characteristics of the patient population [156]

	N / Average	% / SD
Total	312	100%
Gender		
Female	219	70.19%
Male	93	29.81%
Age (years)	27.1	14.0
18-24	59	18.91%
25-34	98	31.41%
35-44	73	23.40%
45-54	68	21.79%
55+	14	4.49%
Place of residence		
Capital	93	29.81%
County town	69	22.12%
Other town	76	24.36%
Village	74	23.72%
Highest level of education		
Primary and vocational school	39	12.50%
Secondary school	116	37.18%
College/university	157	50.32%
Employment		
Employed	230	73.72%
Not employed	82	26.28%
Number of comorbidities		
0	33	10.58%
1	74	23.72%
2-3	101	32.37%
4+	104	33.33%
General health status		
Excellent health	20	6.41%
Good health	76	24.36%
Fair health	141	45.19%
Poor & very poor health	75	24.04%
Symptoms during last week		
No symptoms	90	28.85%
Symptoms	222	71.15%

4.1. Preference elicitation study

4.1.1. VAS, TTO and WTP values

The distribution of VAS, TTO and WTP values is depicted in Figure 2. Mean VAS values for current health, 'CD with strict adherence to GFD', 'CD with loose adherence to GFD' and 'CD without GFD' hypothetical health states 79.69±18.52, 85.36±16.18, 62.44±19.91 and 36.69±25.83, respectively (Table 3). Corresponding mean TTO utilities were higher: 0.90±0.19, 0.91±0.20, 0.87±0.23 and 0.76±0.29. A total of 188 patients (60.3%) were not willing to give up any time for their current health, and there were 73 patients (23.4%) who refused to trade life years in any of the four TTO tasks (non-traders). Overall, 1.3%, 2.6%, 2.2%, and 6.4% of the patients traded all the 10 years for the current health, 'CD with strict adherence to GFD', 'CD with loose adherence to GFD' and 'CD without GFD' hypothetical health states.

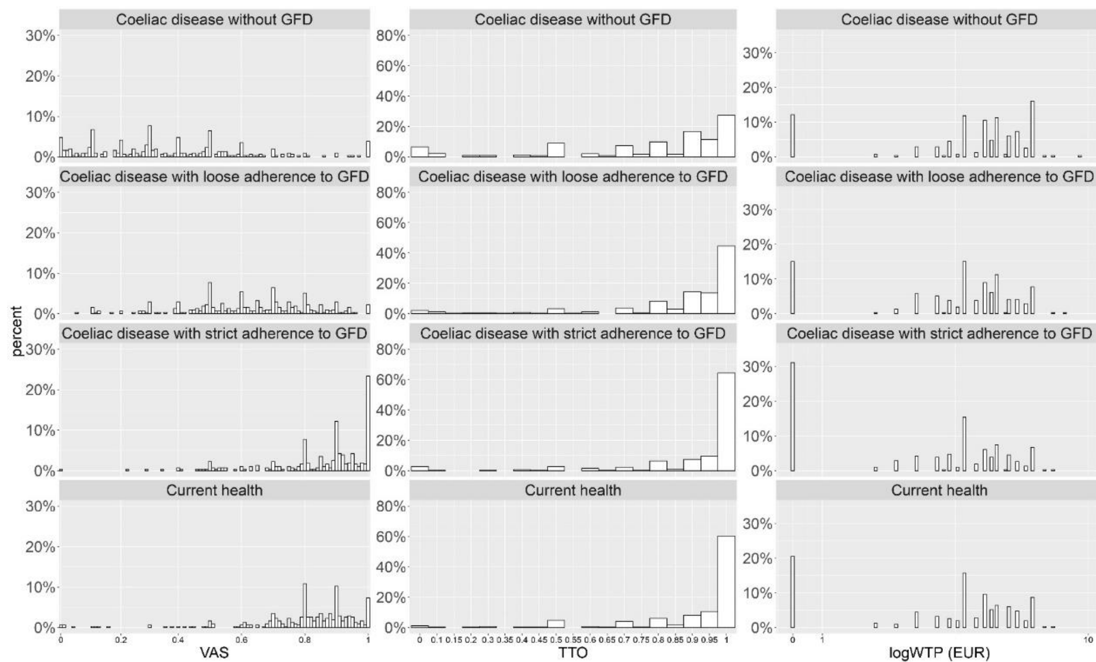

Figure 2. Distribution of VAS, TTO and WTP responses for four CD health states [156]

Abbreviations. VAS: Visual Analogue Scale, TTO: Time trade-off, WTP: Willingness to pay

Table 3. Descriptive statistics of the VAS and TTO utilities and WTP values [156]

Out-come	Health state	N (missing)	Mean	SD	Quartiles			'0' answers* (%)	Maximum answers** (%)
					Q1	Median	Q3		
VAS	Own health	312	79.69	18.52	75	83.50	90.00	0.6	7.4
	CD with strict adherence to GFD	312	85.36	16.18	80	90	98.75	0.3	23.4
	CD with loose adherence to GFD	312	62.44	19.91	50	64.5	77	0	2.2
	CD without GFD	312	36.69	25.83	15	31	50	4.8	3.9
TTO	Own health	312	0.90	0.19	0.9	1	1	1.3	60.3
	CD with strict adherence to GFD	312	0.91	0.20	0.9	1	1	2.6	64.4
	CD with loose adherence to GFD	312	0.87	0.23	0.85	0.95	1	2.2	44.6
	CD without GFD	312	0.76	0.29	0.70	0.90	1	6.4	27.2
WTP (EUR/ year)	Own health	302 (10)	845	1077	66	332	997	20.5	9.3
	CD with strict adherence to GFD	311 (1)	648	1002	0	332	831	31.1	7.4
	CD with loose adherence to GFD	308 (4)	862	1135	133	499	997	15.1	8.3
	CD without GFD	305 (7)	1251	1496	299	831	1994	12.2	17.0

Abbreviations. TTO: time trade-off; VAS: visual analogue scale; WTP: willingness to pay

* equal to 0 value in VAS, trading all the 10 years in TTO, €0 responses in WTP

**equal to 100 value in VAS, trading 0 years in TTO, maximum annual amount in WTP (1 200 000 HUF – €3324 or above)

Currency change: EUR 1 = HUF 361.01

Of the 1248 WTP responses given in the four tasks, 22 (1.8%) nonsensical answers (from 13 patients) were excluded. The mean annual WTP values were €845±1077 for current health, €648±1002 for the 'CD with strict adherence to GFD' health state, €862±1135 for the 'CD with loose adherence to GFD' health state and €1251±1496 for 'CD without GFD' health state (Table 3.). Overall, 79.5%, 68.9%, 84.9% and 87.8% were willing to pay to regain full health. The maximum WTP was €16,620 annually ('CD without GFD health state). A total of 20 patients (6.4%) refused to pay for any of the health states, including their own health. Using any of the three methods (VAS, TTO and WTP), there was a statistically significant difference across patients' valuations for the four health states ($p<0.001$).

4.2.2. Predictors of current own health VAS, TTO and WTP values

The multivariate regressions showed that patients with higher income had significantly higher VAS values ($p=0.006$) (Table 4). A one-point increase in GSRS score (indicating worse HRQoL) was associated with an average decrease of 0.421 ($p<0.001$), and a 1-year older age at diagnosis with a 0.173 decrease in VAS values ($p<0.05$). Concomitant depression and rheumatic disease substantially reduced patients' VAS values (−10.373 and −12.197 $p<0.05$). These variables together explained 30.9% of the overall variation in VAS values.

Females were willing to trade less life years, resulting in higher TTO utilities ($p<0.05$) (Table 4). Similar to VAS, a one-point increase in GSRS resulted in a 0.004 decrease in TTO utilities ($p=0.005$). These three variables explained 8.6% of the variance of TTO utilities.

The amount patients were willing to pay decreased by 70.45% in females compared to males ($p=0.022$). Patients' WTP increased by 6.8% with +1 GSRS score ($p=0.002$), by 3.9% with a one-year increase in age at diagnosis ($p=0.047$) and by 251.6% in case of concomitant gastroesophageal reflux disease ($p=0.012$) (Table 5). A 1% increase in the household's per capita net annual income was associated with an 1.33% increase in the willingness-to-pay amount, on average ($p<0.001$).

4.2.3. Predictors of VAS, TTO and WTP values for hypothetical CD health states

Both the 'CD without GFD' and the 'CD with loose adherence to GFD' hypothetical health states were associated with significantly lower VAS and TTO and higher WTP valuations compared to the 'CD with strict adherence to GFD' health state ($p<0.05$) (Tables 4 and 5). A +1 GSRS score, indicating worse HRQoL was associated with a 0.168-point decrease in VAS values and with a 4.9% increase in the WTP amount ($p<0.05$). Having rheumatic or inflammatory bowel disease decreased the patients' VAS valuations and having higher income resulted in higher TTO and WTP values ($p<0.05$). Furthermore, every one-year increase in the patients' age increased the TTO utility by 0.002 ($p=0.045$). These variables explained 49.0%, 8.7% and 10.9% of the overall variation in VAS, TTO and WTP values, respectively.

Table 4. Predictors of the VAS and TTO utilities [156]

VAS	Coefficient (ß)	SE	p-value
Current health (dependent variable: EQ VAS values): linear regression, n=260 R^2=0.309			
Constant	62.492	13.848	<0.001
Household's per capita net annual income (EUR, logarithm)	3.986	1.431	0.006
GSRS score	-0.421	0.119	<0.001
Age at diagnosis (years)	-0.173	0.077	0.026
Comorbidity: depression	-10.373	4.593	0.025
Comorbidity: rheumatic disease	-12.197	5.170	0.019
Hypothetical health states (dependent variable VAS): random-intercept regression, n=312, R^2=0.490			
Constant	91.015	2.240	<0.001
Hypothetical health states			
'CD without GFD' health state	-48.673	1.530	<0.001
'CD with loose adherence to GFD' health state	-22.917	1.530	<0.001
Individual characteristics			
GSRS score	-0.168	0.070	0.016
Comorbidity: rheumatic disease	-5.872	2.688	0.029
Comorbidity: inflammatory bowel disease	-8.763	4.200	0.037
TTO	**Coefficient (ß)**	**SE**	**p-value**
Current health (dependent variable: years of TTO): linear regression, n=260 R^2=0.0856			
Constant	0.609	0.198	0.002
Female	0.068	0.024	0.005
Household's per capita net annual income (EUR, logarithm)	0.039	0.020	0.055
GSRS score	-0.004	0.001	0.005
Hypothetical health states (dependent variable TTO): random-intercept regression, n=260, R^2=0.0873			
Constant	0.380	0.167	0.024
Hypothetical health states			
'CD without GFD' health state	-0.145	0.015	<0.001
'CD with loose adherence to GFD' health state	-0.038	0.015	0.011
Individual characteristics			
Household's per capita net annual income (EUR, logarithm)	0.050	0.018	0.004
Age (years)	0.002	0.001	0.045

Abbreviations. GSRS: Gastrointestinal Symptom Rating Scale; TTO: time trade-off; VAS: visual analogue scale; WTP: willingness to pay

Table 5. Predictors of WTP responses [156]

	Coefficient (ß)	SE	p-value	% Change effect
Current health (dependent variable: logarithm of WTP): log-linear model, n=253 R^2=0.145				
Constant	-9.887	3.460	0.005	-
Individual characteristics				
Female	-1.219	0.527	0.022	-70.454
Household's per capita net annual income (EUR, logarithm)	1.331	0.352	<0.001	-
GSRS score	0.066	0.021	0.002	6.842
Age at diagnosis (years)	0.038	0.019	0.047	3.894
Comorbidity: gastroesophageal reflux disease	1.257	0.498	0.012	251.614
Hypothetical health states (dependent variable logarithm of WTP): random-intercept log-linear model, n=259, R^2=0.109				
Constant	-10.400	2.765	<0.001	-
Hypothetical health states				
'CD without GFD' health state	2.020	0.230	<0.001	653.811
'CD with loose adherence to GFD' health state	1.482	0.229	<0.001	340.335
Individual characteristics				
Household per capita net annual income (EUR, logarithm)	1.393	0.291	<0.001	-
GSRS score	0.048	0.017	0.005	4.937

Abbreviations. GSRS: Gastrointestinal Symptom Rating Scale; TTO: time trade-off; WTP: willingness to pay

4.2. EQ-5D-5L bolt-on study

4.2.1. Distributional characteristics, ceiling and informativity

The distribution of responses to the EQ-5D-5L dimensions and bolt-ons is shown in Table 6. Among the five core dimensions, SC demonstrated the highest ceiling (98.1%), followed by MO (82.7%), UA (77.9%), AD (59.0%), and PD (58.7%). For all but one of the bolt-ons (CO), the ceiling was lower than that of any of the five core EQ-5D-5L dimensions. Based on the ceiling, the order of the bolt-ons was as follows: TI (22.8%), GI (39.1%), SL (44.6%), DI (52.9%), and CO (74.0%). The ceiling of the EQ-5D-5L was 38.8% (i.e. proportion of 11111 profiles). Adding the TI, SL, GI, DI and CO individual bolt-ons reduced the ceiling to 17.0%, 23.1%, 24.0%, 26.3% and 36.5%, respectively. When adding all five bolt-ons to the EQ-5D-5L, the ceiling was reduced to 7.4%. The

number of profiles significantly increased by adding bolt-ons to the EQ-5D-5L, with the largest increase observed with DI, where the number of profiles nearly doubled.

Table 6. Responses on the five EQ-5D-5L dimensions and five bolt-ons [157]

Dimensions	No problems		Slight problems		Moderate problems		Severe problems		Extreme problems/ unable to	
	n	%	n	%	n	%	n	%	n	%
Mobility (MO)	258	82.7%	39	12.5%	12	3.8%	3	1.0%	0	0.0%
Self-care (SC)	306	98.1%	5	1.6%	1	0.3%	0	0.0%	0	0.0%
Usual activities (UA)	243	77.9%	58	18.6%	6	1.9%	5	1.6%	0	0.0%
Pain/discomfort (PD)	183	58.7%	99	31.7%	24	7.7%	5	1.6%	1	0.3%
Anxiety/depression (AD)	184	59.0%	95	30.4%	24	7.7%	6	1.9%	3	1.0%
Cognition (CO)	231	74.0%	65	20.8%	13	4.2%	3	1.0%	0	0.0%
Dining (DI)	165	52.9%	77	24.7%	57	18.3%	11	3.5%	2	0.6%
Gastrointestinal problems (GI)	122	39.1%	120	38.5%	62	19.9%	7	2.2%	1	0.3%
Sleep (SL)	139	44.6%	119	38.1%	39	12.5%	14	4.5%	1	0.3%
Tiredness (TI)	71	22.8%	148	47.4%	75	24.0%	14	4.5%	4	1.3%

All bolt-ons, except CO demonstrated both a higher absolute and relative informativity than any of the five core dimensions (Table 7). The TI and GI bolt-on items showed the highest relative informativity. Absolute informativity increased with the addition of any of the five bolt-ons to the EQ-5D-5L (from 3.71 to 4.33-4.95). Moreover, relative informativity also increased with the addition of the bolt-ons, except for CO. The highest improvement in relative informativity was achieved by adding the DI bolt-on. Absolute informativity increased with adding an increasing number of bolt-ons; however, relative informativity increased only up to four bolt-ons.

Table 7. Ceiling, informativity and total number of health profiles on EQ-5D-5L and bolt-ons [157]

Dimensions	Ceiling		Ceiling on all five dimensions		Absolute ceiling reduction (%)	Relative ceiling reduction (%)	
EQ-5D-5L	n	%	n	%			
Mobility (MO)	258	82.7%	121	38.8%	-	-	
Self-care (SC)	306	98.1%			-	-	
Usual activities (UA)	243	77.9%			-	-	
Pain/ discomfort (PD)	183	58.7%			-	-	
Anxiety/ depression (AD)	184	59.0%			-	-	
(EQ-5D-5L+) bolt-ons	Ceiling		Ceiling EQ-5D-5L + bolt-on(s)		Absolute ceiling reduction (%)	Relative ceiling reduction (%)	
	n	%	n	%			
Dining (DI)	165	52.9%	82	26.3%	-12.5%	32.2%	
Gastrointestinal problems (GI)	122	39.1%	75	24.0%	-14.7%	38.0%	
Cognition (CO)	231	74.0%	114	36.5%	-2.2%	5.8%	
Sleep (SL)	139	44.6%	72	23.1%	-15.7%	40.5%	
Tiredness (TI)	71	22.8%	53	17.0%	-21.8%	56.2%	
Combinations of bolt-ons							
GI+TI	45	14.4%	37	11.9%	-26.9%	69.4%	
GI+TI+SL	32	10.3%	28	9.0%	-29.8%	76.9%	
GI+TI+SL+DI	26	8.3%	23	7.4%	-31.4%	81.0%	
All five bolt-ons	26	8.3%	23	7.4%	-31.4%	81.0%	
Dimensions	Item-level informativity		Informativity on all five dimensions		Total number of health state profiles		
EQ-5D-5L	H'	J'	H'	J'	Observed (n)	%	Theoretical maximum
Mobility (MO)	0.85	0.36	3.71	0.32	47	1.50%	3125
Self-care (SC)	0.15	0.06					
Usual activities (UA)	0.94	0.40					
Pain/ discomfort (PD)	1.38	0.60					
Anxiety/ depression (AD)	1.43	0.62					
Bolt-ons	Item-level informativity		Informativity on EQ-5D-5L + bolt-on(s)		Total number of health state profiles		
	H'	J'	H'	J'	Observed (n)	%	Theoretical maximum
Dining (DI)	1.65	0.71	4.95	0.36	90	0.58%	15625
Gastrointestinal problems (GI)	1.67	0.72	4.84	0.35	81	0.52%	15625
Cognition (CO)	1.05	0.45	4.33	0.31	75	0.48%	15625
Sleep (SL)	1.65	0.71	4.94	0.35	85	0.54%	15625
Tiredness (TI)	1.77	0.76	4.88	0.35	80	0.51%	15625
EQ-5D-5L+DI+SL	-	-	5.91	0.36	130	0.17%	78125
EQ-5D-5L+DI+SL+GI	-	-	6.63	0.36	169	0.04%	390625
EQ-5D-5L+DI+SL+GI+TI	-	-	7.18	0.34	208	0.01%	1953125
EQ-5D-5L+5 bolt-ons	-	-	7.28	0.31	219	0.00%	9765625

4.2.2. Convergent and divergent validity

The correlations between the EQ-5D-5L, EQ VAS, bolt-ons and GSRS domains and total score are shown in Table 8. In line with our hypotheses, a moderate correlation was observed between GI and PD (rs=0.508), between TI and PD (rs=0.465) and between TI and AD (rs=0.425). The GI bolt-on was strongly correlated with GSRS total score (rs=0.712) and moderately with each GSRS domain (range of rs: 0.419 to 0.584) as expected. The CO, DI and SL bolt-ons exhibited only weak or very weak correlations with any of the five core dimensions of the EQ-5D-5L.

Table 8. Convergent and divergent validity of the EQ-5D-5L and five bolt-ons [157]

Variables	EQ-5D-5L					Bolt-ons					EQ VAS	GSRS total score	GSRS Diarr-hoea	GSRS Indi-gestion	GSRS Consti-pation	GSRS Abdo-minal pain
	Mobility	Self-care	Usual activities	Pain/ discomfort	Anxiety/ depression	Dining	Gastro-intest. prob.	Cog-nition	Sleep	Tired-ness						
Mobility	-															
Self-care	0.285	-														
Usual activities	0.429	0.300	-													
Pain/discomfort	0.365	0.240	0.499	-												
Anxiety/ depression	0.159	0.174	0.273	0.407	-											
Dining	0.163	0.098*	0.333	0.283	0.271	-										
Gastrointestinal problems	0.200	0.103*	0.357	0.508	0.372	0.383	-									
Cognition	0.165	-0.016*	0.391	0.374	0.365	0.326	0.369	-								
Sleep	0.202	0.087*	0.269	0.335	0.294	0.245	0.309	0.314	-							
Tiredness	0.313	0.136	0.390	0.465	0.425	0.355	0.403	0.399	0.376	-						
EQ VAS	-0.329	-0.193	-0.424	-0.542	-0.317	-0.229	-0.504	-0.347	-0.262	-0.388	-					
GSRS total score	0.222	0.139	0.376	0.534	0.344	0.359	0.712	0.331	0.364	0.492	-0.462	-				
GSRS Diarrhoea	0.161	0.071*	0.286	0.370	0.227	0.326	0.467	0.221	0.264	0.304	-0.264	0.650	-			
GSRS Indigestion	0.126	0.069*	0.222	0.342	0.234	0.269	0.565	0.226	0.261	0.426	-0.373	0.815	0.435	-		
GSRS Constipation	0.147	0.102*	0.314	0.365	0.248	0.190	0.419	0.288	0.292	0.250	-0.248	0.660	0.358	0.430	-	
GSRS Abdominal pain	0.193	0.075*	0.386	0.484	0.295	0.350	0.584	0.315	0.291	0.431	-0.403	0.808	0.433	0.567	0.447	-
GSRS Reflux	0.246	0.128	0.312	0.497	0.308	0.231	0.478	0.246	0.359	0.397	-0.358	0.650	0.330	0.356	0.372	0.553

Abbreviations. GSRS: Gastrointestinal Symptoms Rating Scale, EQ VAS: EQ Visual Analogue Scale

*p ≥ 0.05

4.2.3. Known-group validity

The addition of the GI bolt-on significantly improved the ability of the EQ-5D-5L to discriminate between groups of patients based on self-perceived health status, GSRS tertiles and the presence of symptoms, with relative efficiencies ranging between 1.30 (95%CI 1.14-1.49) and 1.84 (95%CI 1.56-2.23) (Table 9). After the inclusion of the GI bolt-on, no additional bolt-ons were able to further improve the known-group validity of the instrument.

Table 9. Known groups validity of the EQ-5D-5L plus bolt-ons [157]

Health and quality of life	**Mean (SD) EQ-5D-5L+bolt-on LSS (0-100)**			**RE (95%CI), ref: previous row**
Health status	**Poor-fair**	**Good**	**Very good-excellent**	
n	75	141	96	-
EQ-5D-5L	17.6 (14.25)	6.81 (7.45)	2.45 (4.04)	-
EQ-5D-5L+GI	20.83 (13.44)	9.31 (7.69)	3.56 (4.87)	1.30 (1.14-1.49)
Gastrointestinal symptoms (GSRS tertiles)[a]	**<21**	**22-30**	**30+**	-
n	111	99	102	-
EQ-5D-5L	3.24 (5.59)	6.97 (6.84)	14.36 (13.94)	-
EQ-5D-5L+GI	3.75 (5.36)	9.43 (7.16)	18.30 (13.05)	1.84 (1.56-2.23)
Symptomatic	**No symptoms**		**At least one symptom**	
n	90		222	-
EQ-5D-5L	3.00 (7.10)		10.11 (10.99)	-
EQ-5D-5L+GI	3.56 (6.45)		13.04 (11.11)	1.79 (1.49-2.44)

Abbreviations. CI: confidence interval; GI: gastrointestinal problems bolt-on; GSRS: Gastrointestinal Symptoms Rating Scale; LSS: level sum score

a: Higher scores represent worse gastrointestinal symptoms

4.2.4. Exploratory power

The results of the univariable linear regression analysis revealed that UA (adjusted R^2=0.304) and PD (adjusted R^2=0.301) demonstrated the highest explanatory power for EQ VAS scores (Table 10). The CO (adjusted R^2=0.196) and GI (adjusted R^2=0.179) bolt-ons performed the best among the bolt-ons. With regard to SWLS, AD (adjusted R^2=0.140) and PD (adjusted R^2=0.116) exhibited the highest explanatory power, while TI (adjusted R^2=0.103) and GI (adjusted R^2=0.095) demonstrated the highest values among the bolt-ons. The addition of bolt-ons to the EQ-5D-5L improved the explained variance of EQ VAS and SWLS scores, as indicated by adjusted R^2. Specifically, two bolt-ons (GI and CO) improved the explained variance in EQ VAS from 0.411 to 0.440, while three bolt-ons (DI, GI and SL) improved the explained variance in SWLS from 0.193 to 0.206. When adjusting the models for age, gender and GSRS score, there were

only minimal differences in the best-performing bolt-ons, and the contributions of CO and GI to explaining health (EQ VAS) and DI to well-being (SWLS) were confirmed.

Table 10. The explanatory power of EQ-5D-5L and bolt-ons for EQ VAS and SWLS [157]

Dimensions	EQ VAS		Dimensions	SWLS	
	Adjusted R^2	ΣΔ adjusted R^2		Adjusted R^2	ΣΔ adjusted R^2
Individual dimensions			**Individual dimensions**		
Mobility (MO)	0.1587	-	Mobility (MO)	0.0345	-
Self-care (SC)	0.0886	-	Self-care (SC)	0.0044	-
Usual activities (UA)	0.3039	-	Usual activities (UA)	0.1101	-
Pain/discomfort (PD)	0.3012	-	Pain/discomfort (PD)	0.1156	-
Anxiety/depression (AD)	0.1826	-	Anxiety/depression (AD)	0.1399	-
Gastrointestinal problems (GI)	0.1787	-	Gastrointestinal problems (GI)	0.0954	-
Cognition (CO)	0.1958	-	Cognition (CO)	0.0950	-
Sleep (SL)	0.1085	-	Sleep (SL)	0.0718	-
Tiredness (TI)	0.1617	-	Tiredness (TI)	0.1029	-
Dining (DI)	0.0652	-	Dining (DI)	0.0802	-
EQ-5D-5L (+bolt-ons)			**EQ-5D-5L (+bolt-ons)**		
MO+SC+UA+PD+AD	0.4109	-	MO+SC+UA+PD+AD	0.1934	-
MO+SC+UA+PD+AD+CO	0.4293	0.0184	MO+SC+UA+PD+AD+DI	0.2039	0.0105
MO+SC+UA+PD+AD +CO+GI	0.4402	0.0109	MO+SC+UA+PD+AD+DI+SL	0.2052	0.0013
-	-	-	MO+SC+UA+PD+AD+DI+GI+SL	0.2057	0.0005

Abbreviations. EQ VAS: EQ Visual Analog Scale; SWLS: Satisfaction with Life Scale

4.2.5. Dimensionality

The PCA identified four factors (sorted by descending eigenvalue): ‘gastrointestinal problems’, ‘satisfaction with life’, ‘psychosocial health’ and ‘pain and usual activities’. These factors explained 61.9% of the total variance. The GSRS domains and GI bolt-on loaded onto the ‘gastrointestinal problems’ factor, while the remaining four bolt-ons along with the EQ-5D-5L AD item loaded onto the ‘psychosocial health’ factor. All five SWLS items loaded onto the ‘satisfaction with life’ factor, whereas the ‘pain and usual activities’ factor was constituted by the first four EQ-5D-5L items. The EQ-5D-5L PD item was loaded on both the ‘gastrointestinal problems’ and ‘pain and usual activities’ factors, with a higher factor loading for the latter. The CFA confirmed the results of PCA

in terms of the number of factors identified and the relationships between items and factors (Table 11). The model showed an appropriate fit with an RMSEA of 0.064 and CFI of 0.927. All but two items (EQ-5D-5L SC and DI bolt-on) had a standardised factor loading of >0.55, suggesting a good fit. Only the GI bolt-on loaded on a completely different factor than any EQ-5D-5L item; the other four bolt-ons were loaded on the same 'psychosocial health' factor as the EQ-5D-5L AD item.

Table 11. Standardised factor loadings in the confirmatory factor analysis [157]

Items	Loadings per factors			
	1. Gastro-intestinal problems	2. Satis-faction with life	3. Psycho-social health	4. Pain and usual activities
GSRS Abdominal pain	0.826	-	-	-
EQ-5D-5L Gastrointestinal problems bolt-on	0.762	-	-	-
GSRS Indigestion	0.711	-	-	-
GSRS Reflux	0.684	-	-	-
GSRS Constipation	0.620	-	-	-
GSRS Diarrhoea	0.593	-	-	-
SWLS The conditions of my life are excellent.	-	0.884	-	-
SWLS So far I have gotten the important things I want in life	-	0.851	-	-
SWLS I am satisfied with my life.	-	0.794	-	-
SWLS In most ways my life is close to my ideal.	-	0.792	-	-
SWLS If I could live my life over, I would change almost nothing	-	0.714	-	-
EQ-5D-5L Tiredness bolt-on	-	-	0.711	-
EQ-5D-5L Sleep bolt-on	-	-	0.679	-
EQ-5D-5L Cognition bolt-on	-	-	0.613	-
EQ-5D-5L Anxiety/depression	-	-	0.574	-
EQ-5D-5L Dining bolt-on	-	-	0.523	-
EQ-5D-5L Pain/discomfort	-	-	-	0.776
EQ-5D-5L Usual activities	-	-	-	0.773
EQ-5D-5L Mobility	-	-	-	0.590
EQ-5D-5L Self-care	-	-	-	0.454

Abbreviations. GSRS: Gastrointestinal Symptoms Rating Scale, SWLS: Satisfaction with Life Scale

4.3. ICECAP-A psychometric testing study

4.3.1. Distributional characteristics

The greatest reported limitations on the ICECAP-A were found in the attributes of stability and achievement, with 81% and 78% of respondents, respectively (Figure 3). The attributes with the highest ceiling (i.e., proportion of 'full capability') were attachment (49%), enjoyment (42%), and autonomy (37%). For the EQ-5D-5L, most respondents reported no problems in self-care (98%) and mobility (83%). However, substantial proportions reported issues in the pain/discomfort and anxiety/depression dimensions (both 41%).

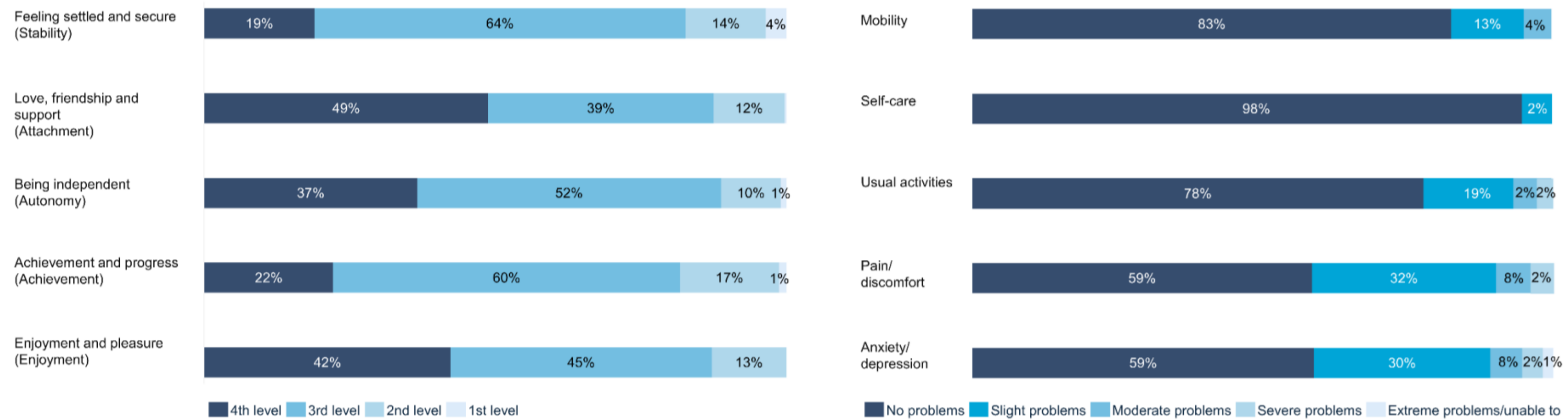

Figure 3. Comparison of ICECAP-A attribute and EQ-5D-5L dimension responses in coeliac disease [188]

Bar lengths are not to scale for values below 4% to improve visibility

Abbreviations. ICECAP-A: ICEpop CAPability measure for Adults

At the instrument level, the mean ICECAP-A index value was 0.85 (SD=0.17), with only 6.7% of respondents reaching the maximum score of 1.0, indicating the absence of ceiling effect (Figure 4). The EQ-5D-5L index value averaged 0.92 (SD=0.13) and demonstrated a pronounced ceiling effect, with 38.8% of respondents achieving the maximum score. The mean EQ VAS score was 79.69 (SD=18.52).

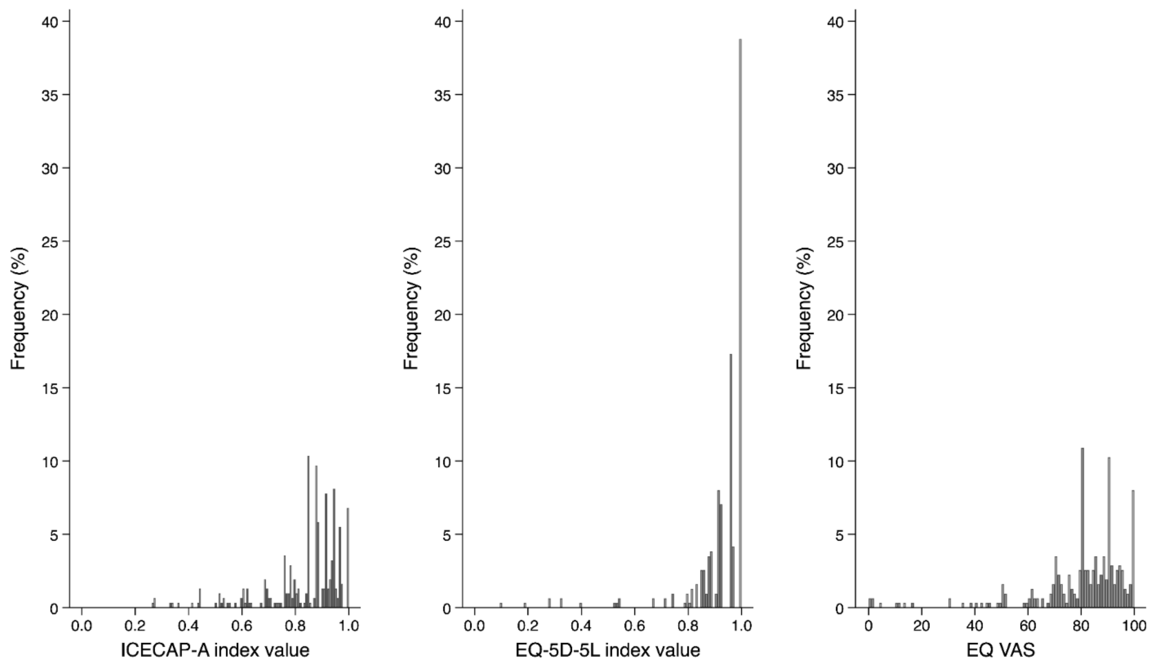

Figure 4. Distribution of ICECAP-A and EQ-5D-5L index values and EQ VAS scores [188]

Abbreviations. ICECAP-A: ICEpop CAPability measure for Adults, EQ VAS: EQ Visual Analogue Scale

ICECAP-A index values decreased from 0.87 among respondents aged 25–34 to 0.77 among those aged 55 and older (Figure 5). EQ-5D-5L index values showed a similar trend, declining from 0.94 among the youngest group (aged 18-24) to 0.85 in the oldest. Likewise, EQ VAS scores fell from 83.80 in the youngest group to 61.79 in the oldest.

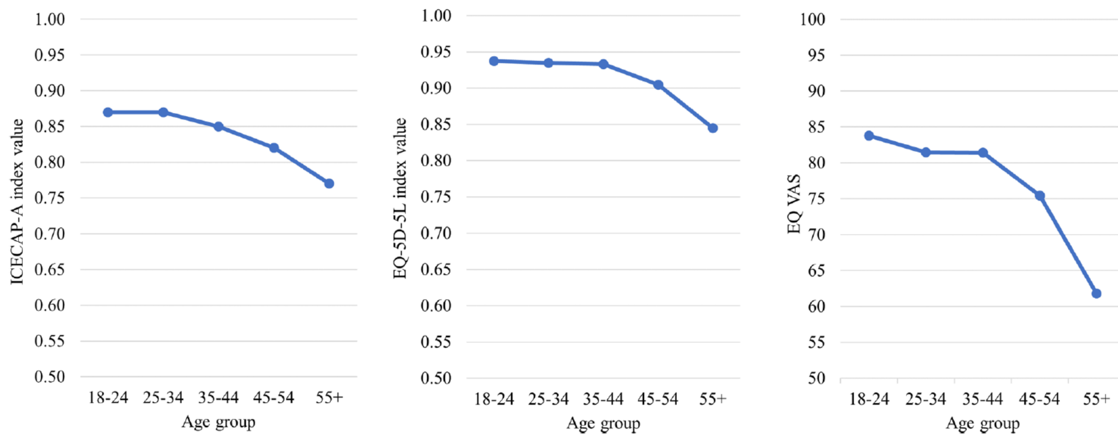

Figure 5. Mean ICECAP-A and EQ-5D-5L index values, and EQ VAS scores by age group [188]

Abbreviations. ICECAP-A: ICEpop CAPability measure for Adults, EQ VAS: EQ Visual Analogue Scale

4.3.2. Known-group validity

The ICECAP-A index values differentiated between several predefined groups (Table 12). Significant differences were observed across CD-related variables (symptoms during the last week, GSRS tertiles, and GFD duration), clinical variables (general health status and comorbidities), and sociodemographic characteristics (employment, education, and place of residence). EQ-5D-5L and EQ VAS consistently showed larger effect sizes than ICECAP-A for CD-related and clinical variables. For CD-related variables, GSRS tertiles produced moderate effect sizes across all outcome measures: ICECAP-A (η^2=0.065), EQ-5D-5L (η^2=0.134) and EQ VAS (η^2=0.138). Symptoms during the last week were associated with small effect sizes for both ICECAP-A (d=0.379) and EQ-5D-5L (d=0.496), but a moderate effect size for EQ VAS (d=0.628). GFD duration showed small but statistically significant effect sizes: ICECAP-A (η^2=0.046), EQ-5D-5L (η^2=0.026) and EQ VAS (η^2=0.040). General health status showed large effect sizes for all measures: ICECAP-A (η^2=0.189), EQ-5D-5L (η^2=0.215) and EQ VAS (η^2=0.353). A similar pattern was seen for comorbidities, with ICECAP-A (η^2=0.073) and EQ-5D-5L (η^2=0.120) showing moderate effect sizes, while EQ VAS (η^2=0.159) reached a large effect size.

For socioeconomic characteristics, ICECAP-A showed small effect sizes for education (η^2=0.032) and place of residence (η^2=0.035), whereas EQ-5D-5L and EQ VAS showed only trivial effect sizes (η^2<0.02). Neither ICECAP-A nor EQ-5D-5L differentiated by age or gender, while EQ VAS detected a moderate effect size for age (η^2=0.068) and small effect size for gender (d=0.334).

Table 12. ICECAP-A, EQ-5D-5L, and EQ VAS scores by sociodemographic and clinical characteristics [188]

Characteristics of the patient population			ICECAP-A index value[a]		P value	Effect size	EQ-5D-5L index value[a]		P value	Effect size	EQ VAS		P value	Effect size
	N	%	Mean	SD			Mean	SD			Mean	SD		
Total	312	100%	0.85	0.16			0.92	0.13			79.69	18.52		
Gender														
Female	219	70.19%	0.85	0.17	0.540	d=0.076	0.92	0.14	0.071	d=0.225	77.87	19.91	0.002	d=0.334
Male	93	29.81%	0.86	0.15			0.94	0.10			83.99	13.94		
Age (years)														
18-24	59	18.91%	0.87	0.15	0.167	η^2=0.021	0.94	0.11	0.070	η^2=0.028	83.80	14.24	<0.001	η^2=0.068
25-34	98	31.41%	0.87	0.15			0.93	0.12			81.47	16.33		
35-44	73	23.40%	0.85	0.17			0.93	0.11			81.41	14.96		
45-54	68	21.79%	0.82	0.18			0.90	0.15			75.41	23.50		
55+	14	4.49%	0.77	0.17			0.85	0.20			61.79	25.86		
Place of residence														
Capital	93	29.81%	0.88	0.13	0.013	η^2=0.035	0.93	0.10	0.235	η^2=0.014	82.14	12.32	0.128	η^2=0.018
County town	69	22.12%	0.88	0.14			0.94	0.08			81.70	17.90		
Other town	76	24.36%	0.82	0.20			0.90	0.17			76.05	24.94		
Village	74	23.72%	0.82	0.17			0.91	0.14			78.49	17.50		
Highest level of education														
Primary and vocational school	39	12.50%	0.79	0.20	0.017	η^2=0.032	0.90	0.16	0.561	η^2=0.007	73.85	22.94	0.160	η^2=0.017
Secondary school	116	37.18%	0.83	0.19			0.92	0.14			79.44	21.77		
College/university	157	50.32%	0.88	0.13			0.93	0.11			81.33	13.97		
Employment														
Employed	230	73.72%	0.86	0.15	0.011	d=0.328	0.93	0.11	0.092	d=0.217	80.11	18.07	0.507	d=0.085

Characteristics of the patient population			ICECAP-A index value[a]		P value	Effect size	EQ-5D-5L index value[a]		P value	Effect size	EQ VAS		P value	Effect size
	N	%	Mean	SD			Mean	SD			Mean	SD		
Not employed	82	26.28%	0.81	0.20			0.90	0.17			78.52	19.80		
Number of comorbidities														
0	33	10.58%	0.88	0.13	<0.001	η^2=0.073	0.98	0.03	<0.001	η^2=0.120	89.48	10.77	<0.001	η^2=0.159
1	74	23.72%	0.91	0.09			0.97	0.05			85.58	9.64		
2-3	101	32.37%	0.85	0.16			0.93	0.13			82.51	13.66		
4+	104	33.33%	0.79	0.19			0.87	0.16			69.65	24.24		
General health status														
Excellent health	20	6.41%	0.92	0.12	<0.001	η^2=0.189	1.00	0.01	<0.001	η^2=0.215	96.90	4.80	<0.001	η^2=0.353
Good health	76	24.36%	0.91	0.09			0.97	0.04			89.87	6.95		
Fair health	141	45.19%	0.87	0.13			0.94	0.08			81.19	12.84		
Poor & very poor health	75	24.04%	0.73	0.22			0.82	0.20			61.97	23.80		
Symptoms during last week														
No symptoms	90	28.85%	0.89	0.13	0.001	d=0.379	0.97	0.11	<0.001	d=0.496	87.67	12.04	<0.001	d=0.628
Symptoms	222	71.15%	0.83	0.17			0.91	0.13			76.46	19.70		
GSRS tertiles														
≤ 21	111	35.58%	0.90	0.12	<0.001	η^2=0.065	0.97	0.08	<0.001	η^2=0.134	86.86	14.01	<0.001	η^2=0.138
22 - 30	99	31.73%	0.85	0.15			0.94	0.06			81.21	13.01		
31+	102	32.69%	0.80	0.20			0.86	0.18			70.41	23.08		
GFD duration														
less than a year	29	9.29%	0.75	0.22	0.002	η^2=0.046	0.88	0.16	0.044	η^2=0.026	69.34	26.65	0.005	η^2= 0.040
1-5 years	109	34.94%	0.85	0.16			0.91	0.16			78.55	17.42		
6-10 years	71	22.76%	0.88	0.14			0.95	0.06			82.42	14.16		

Characteristics of the patient population			ICECAP-A index value[a]		P value	Effect size	EQ-5D-5L index value[a]		P value	Effect size	EQ VAS		P value	Effect size
	N	%	Mean	SD			Mean	SD			Mean	SD		
more than 10 years	103	33.01%	0.86	0.15			0.93	0.11			81.93	18.72		
Self-reported frequency of dietary errors[b]														
Weekly - monthly	67	21.47%	0.84	0.16	0.214	η^2=0.010	0.94	0.08	0.579	η^2=0.004	80.66	13.56	0.314	η^2=0.008
Quarterly - half yearly	43	13.78%	0.82	0.16			0.94	0.07			83.37	10.53		
Less than half year	192	61.54%	0.86	0.16			0.92	0.15			78.79	21.15		

Abbreviations. d: Cohen's D, η^2: eta-squared, ICECAP-A: ICEpop CAPability measure for Adults, EQ VAS: EQ Visual Analogue Scale, GSRS: Gastrointestinal Symptom Rating Scale, GFD: gluten-free diet

[a]Index values were calculated using the respective Hungarian value sets for the ICECAP-A and EQ-5D-5L

[b]The self-reported frequency of dietary errors among 10 respondents is unknown

4.3.3. Convergent and divergent validity

ICECAP-A attributes demonstrated trivial-to-moderate correlations with EQ-5D-5L dimensions (r_s:=-0.005 to -0.435), with the strongest correlation observed between ICECAP-A stability and EQ-5D-5L anxiety/depression (r_s=-0.435) (Table 13). Correlations between ICECAP-A attributes and SWLS score were stronger (r_s=0.261 to 0.617) than those between EQ-5D-5L dimensions and SWLS score (r_s=-0.089 to -0.364). ICECAP-A attributes also showed weak-to-moderate correlations with GSRS score (r_s=-0.160 to -0.368). The strongest correlations between ICECAP-A attributes and GSRS score were seen for stability (r_s=-0.368) and enjoyment (r_s=-0.264), while EQ-5D-5L dimensions such as pain/discomfort (r_s=0.534) and usual activities (r_s=0.376) showed stronger correlations with GSRS score.

At the instrument level, ICECAP-A index values correlated moderately with the EQ-5D-5L index values (r_p=0.551) and with EQ VAS scores (r_p=0.459). ICECAP-A index values also showed a stronger correlation with SWLS scores (r_s=0.698) than did EQ-5D-5L index values (r_p=0.369). GSRS scores were moderately correlated with EQ-5D-5L index values (r_p=-0.458) and EQ VAS scores (r_p=-0.416), but only weakly with ICECAP-A index values (r_p=-0.284) and SWLS scores (r_p=-0.292).

Table 13. Convergent and divergent validity of the EQ-5D-5L and ICECAP-A [188]

		ICECAP-A index value	ICECAP-A attributes					EQ VAS	EQ-5D-5L index value	EQ-5D-5L dimensions					SWLS
			Stability	Attachment	Autonomy	Achievement	Enjoyment			Mobility	Self-care	Usual activities	Pain / discomfort	Anxiety / depression	
ICECAP-A attribute	Stability	0.709													
	Attachment	0.745	0.382												
	Autonomy	0.538	0.388	0.245											
	Achievement	0.729	0.515	0.413	0.454										
	Enjoyment	0.771	0.520	0.577	0.274	0.515									
EQ VAS		0.459	0.440	0.236	0.195	0.260	0.326								
EQ-5D-5L index value		0.551	0.487	0.329	0.251	0.323	0.463	0.606							
EQ-5D-5L dimensions	Mobility	-0.185	-0.259	-0.104*	-0.082*	-0.113	-0.223	-0.329	-0.477						
	Self-care	-0.135	-0.204	-0.126	-0.156	-0.005*	-0.116	-0.193	-0.240	0.285					
	Usual activities	-0.386	-0.414	-0.236	0.254	-0.323	-0.311	-0.424	-0.591	0.429	0.300				
	Pain / discomfort	-0.374	-0.365	-0.253	-0.171	-0.250	-0.374	-0.542	-0.831	0.365	0.240	0.499			
	Anxiety / depression	-0.419	-0.435	-0.298	-0.273	-0.244	-0.367	-0.317	-0.733	0.159	0.174	0.273	0.407		
SWLS		0.698	0.530	0.521	0.261	0.483	0.617	0.394	0.369	-0.158	-0.089*	-0.294	-0.344	-0.364	
GSRS		-0.284	-0.368	-0.202	-0.160	-0.231	-0.264	-0.416	-0.458	0.222	0.139	0.376	0.534	0.344	-0.292

*p≥ 0.05

Abbreviations. ICECAP-A: ICEpop CAPability measure for Adults, EQ VAS: EQ Visual Analogue Scale, GSRS: Gastrointestinal Symptom Rating Scale; SWLS: Satisfaction with Life Scale

5. Discussion

5.1. Preference elicitation study

The objective of this study was to estimate VAS, TTO and WTP values for both current and hypothetical health states in adults living with CD. This study appears to be the first to report TTO-derived utility estimates obtained directly from patients with CD. The health state representing "CD with strict adherence to GFD" showed lower utility than expected, likely reflecting psychosocial burdens, such as social restrictions related to eating. Older age at diagnosis, male gender, lower income, more severe gastrointestinal symptoms and comorbidities were associated with lower VAS and TTO and/or higher WTP values. More variance was explained in VAS than in TTO or WTP, due to the fact that we did not collect several known predictors of time and monetary trade-offs (e.g., cultural values, self-esteem, marital/parental status, religious, life attitudes) [189-191]. Similarly, WTP values may have various additional predictors, such as sociodemographic characteristics and perceived threats and benefits of treatment [192].

Our findings are consistent with previous research in CD. The mean GSRS total score (28.3) was in the range of other patient populations on GFD from different countries (21.0-30.4) [193, 194]. Women reported more gastrointestinal problems than men, aligned with evidence showing greater HRQoL impairment in females with CD [195-199]. Despite reporting worse symptoms, women were less willing to sacrifice life-years or pay to regain full health. Older age at diagnosis was linked to lower health valuation and greater financial willingness to invest in health improvements, in line with prior literature [194, 200-204]. VAS values in our Hungarian sample were comparable to those from Poland and the UK among highly adherent patient cohorts [129, 137, 152]. Likewise, our hypothetical TTO utilities (0.76 without GFD and 0.91 with strict GFD) reflect previously documented pre-/post-diagnosis changes in EQ-5D index values [129, 137].

Preference-based data offer valuable insights into the burden of CD and enable their use in economic evaluations. Given that generic measures such as EQ-5D may not fully capture CD-specific impacts, directly derived utilities, especially those sensitive to

dietary adherence, may be more appropriate for cost-utility analyses of GFD and future treatments. The high WTP values further suggest strong patient interest in accessible GFD products and novel therapies. These results may support both industry investment decisions and policy considerations aimed at reducing the economic burden of treatment. Utility values can be incorporated into cost-utility analyses through the calculation of QALYs, while WTP estimates can inform cost-benefit evaluations of GFD and emerging therapeutic interventions [205]. Preferences may be derived from the general public or patients. In most European countries, a societal perspective is recommended in the context of economic evaluations in healthcare [206, 207]. However, an increasing body of research advocates considering both patient-derived and general population utilities in economic analyses to capture a more comprehensive view of value [208-210].

Insufficient adherence to a GFD in CD can lead to substantial QALY losses at the population level. Preference-accompanied measures, such as the EQ-5D, may not be able to fully capture the health impact of CD, vignette-based direct utility elicitation may provide a more accurate assessment in this population. In our study, the TTO approach effectively distinguished health states based on levels of dietary adherence. Consequently, directly elicited utilities may be preferable for estimating QALYs. In cost-utility analyses of GFD and new treatments for CD, directly elicited utilities may therefore represent a more appropriate basis to calculate QALYs. Over 10 years, untreated CD may cause a loss of between 1.3 (with loose adherence to GFD, calculated as 10*(1-0.87)) and 2.4 (CD without GFD, calculated as 10*(1-0.76)) QALY per patient. These results underline the considerable health gains achievable through strict dietary adherence and highlight the importance of interventions that improve access to gluten-free food products. The WTP findings also indicate meaningful patient demand for new treatment options, with 69–88% of participants expressing a willingness to pay.

A wide range of reimbursement mechanisms exist internationally to alleviate the financial burden of GFD for individuals with CD, such as tax reduction (Hungary, Canada, the US, the Netherlands and Portugal). In Hungary in 2025, adult CD patients (BNO-code: K900) with taxable income are eligible for a personal income tax deduction of approximately HUF 195,600 annually (based on 5% of the monthly minimum wage) based on the legal

framework of Government Decree No. 335/2009 (XII. 29.) [211]. Other common reimbursement mechanisms include cash transfer (Italy, Argentina, Uruguay, Finland, Greece, France, Norway, Belgium and Slovenia only for children), food provision (some provinces in Argentina and Spain), prescription for gluten-free food (New Zealand, Ireland, the UK) and subsidy (Northern Ireland, Scotland, the Czech Republic) to reduce the individual financial burden of GFD [212, 213]. In contrast, several countries or regions, such as Germany, parts of Spain and Mexico, do not provide any support for GFD products [213]. Our findings may contribute new evidence for relevant national health and social policy programmes affecting the access to gluten-free products.

5.2. EQ-5D-5L bolt-on study

This study evaluated the psychometric performance of two newly developed EQ-5D-5L bolt-on items (dining and gastrointestinal problems) and three existing (cognition, sleep, tiredness) bolt-on items for the EQ-5D-5L in patients with CD. Incorporating any of the five bolt-ons reduced ceiling effects and enhanced the overall informativity of the instrument; however, the cognition item provided only limited additional value within this sample. While the SL and TI bolt-ons exhibited strong descriptive characteristics similarly to earlier studies [68, 214], the GI and DI bolt-ons appeared to perform slightly better in this specific population, which consisted of patients all following a GFD.

The GI bolt-on demonstrated strong overall measurement performance, including strong convergent validity with the GSRS domains and total score, enhanced explanatory power for EQ VAS and significantly improved known-group validity. Importantly, it was the only bolt-on to load onto a distinct factor from the five core EQ-5D-5L dimensions, indicating that it captures a unique aspect of HRQoL not encompassed by the existing descriptive system. However, earlier qualitative and quantitative findings suggest that the impact of gastrointestinal problems can, to some extent, be picked up by the pain/discomfort item [142, 215-217]. This corresponds with our findings, where the correlation between the GI bolt-on and pain/discomfort was moderate (r_s=0.51). Prior studies indicate that respondents frequently interpret the pain/discomfort item primarily as a measure of pain, rather than broader forms of physical discomfort [142, 218, 219]. Bolt-ons that specifically address particular types of discomfort, such as skin irritation, breathing problems or gastrointestinal problems, therefore can enhance the instrument's

content validity and sensitivity [65, 67, 143, 144, 220-222]. While our study confirms the value of the GI bolt-on, future research should further explore potential conceptual overlap with the pain/discomfort dimension and clarify the contexts in which a GI bolt-on contributes the greatest incremental benefit.

The DI bolt-on appeared to add information beyond the core EQ-5D-5L, particularly in relation to subjective well-being. In factor analyses, the DI bolt-on loaded onto the 'psychosocial health' factor alongside the CO, SL and TI bolt-ons, as well as the EQ-5D-5L anxiety/depression dimension, indicating potential partial overlap in constructs. A more comprehensive set of diet- and eating-related items might have yielded a separate dietary factor, as proposed by conceptual models for HRQoL in CD [155]. Once the GI bolt-on was incorporated, DI provided little additional improvement in known-group discrimination, which may be explained by the predominantly symptom- and clinically oriented definitions of the groups examined, rather than psychosocial or well-being domains. Future studies should further evaluate the DI bolt-on in more diverse patient populations and consider expanding the scope of diet-specific content to better capture the broader impact of dietary restrictions in CD.

5.3. ICECAP-A psychometric testing study

This study was the first to evaluate the psychometric properties of the ICECAP-A in individuals with CD and to conduct a direct comparison with the EQ-5D-5L. The ICECAP-A demonstrated strong psychometric performance overall, characterised by the absence of a ceiling effect, comparable known-group validity to the EQ-5D-5L, and convergent validity with the SWLS. Prior research has underscored the limited sensitivity of generic HRQoL instruments, such as the EQ-5D-5L, in capturing the wider impacts of CD, as evidenced by studies from the UK, Poland and Slovenia, where patients with CD reported higher EQ-5D scores than those in the general population [129, 130, 135]. Consistent with previous research, we observed a substantial ceiling effect for the EQ-5D-5L index values, whereas no ceiling effect was detected for the ICECAP-A. Instead, notable limitations in capability were reported across all ICECAP-A attributes. Only 19% of respondents reported full capability in the stability attribute, indicating perceived emotional and environmental insecurity, which is an aspect not directly addressed by HRQoL instruments. These findings highlight the value of ICECAP-A in capturing

broader capability-related aspects of patient experience that may remain limited even when general HRQoL appears overall good. This is particularly important in chronic but manageable conditions such as CD, where individuals may report relatively high HRQoL while still experiencing constraints in some aspects of life.
With respect to known-group validity, the EQ-5D-5L demonstrated a stronger capacity to discriminate between groups defined by CD-specific and clinical characteristics, consistent with its primary focus on HRQoL outcomes. However, its pronounced ceiling effect may limit its ability to detect differences among individuals with relatively good health status. In such higher ranges of functioning, the ICECAP-A may retain greater discriminatory power, as it is not subject to the same measurement constraints. Furthermore, the differing correlation patterns observed for ICECAP-A and EQ-5D-5L reflect their different underlying conceptual foundations. The EQ-5D-5L, as a generic HRQoL measure, primarily captures physical symptoms and functional impairments, which explains its stronger associations with the GSRS. In contrast, the ICECAP-A, designed to measure capability well-being, showed stronger convergence with the SWLS and only moderate correlation with GSRS scores, indicating its ability to capture broader life aspects beyond physical symptoms. In addition to their conceptual differences, the instruments also vary in response structure and framing, which may partly explain the variation in their psychometric performance. For instance, the ICECAP-A is more positively framed than the EQ-5D-5L, encouraging respondents to reflect on capabilities rather than problems. They also differ in the number of response levels per item.

Overall, these findings support the complementary application of ICECAP-A and EQ-5D-5L in health economic evaluation and decision-making. The EQ-5D remains the dominant preference-based HRQoL instrument in cost-utility analyses as it is widely recommended by HTA guidelines in more than 20 countries, including Hungary [30, 60]. Its widespread adoption is supported by the availability of value sets for over 30 countries, enabling standardised QALY calculations [91]. By contrast, ICECAP-A is currently included in only a few HTA guidelines, such as those in the UK and the Netherlands, primarily for assessing non-health effects or non-curative interventions, and value sets for ICECAP-A are also available for only a limited number of countries [47, 48]. Furthermore, unlike the EQ-5D-5L, ICECAP-A does not support the calculation of QALYs, as it is grounded in a capability-based rather than health utility framework.

Combining these instruments can offer a more comprehensive representation of the benefits, capturing both health-related and wider well-being outcomes.

5.4. Limitations

Several limitations should be considered. All data were obtained through an online survey and relied on self-reported diagnoses and symptom information that were not clinically verified. The sample predominantly consisted of respondents with favourable socioeconomic status, potentially leading to selection bias and limited generalisability to the broader Hungarian CD population. Moreover, due to convenience sampling and voluntary participation, individuals with greater engagement in CD management may have been more likely to participate. Furthermore, as the sample comprised only GFD-adherent patients, it was not possible to assess outcomes in untreated populations. All instruments were completed in a fixed order, which may have led to ordering effects in questionnaires completed later. The applied cross-sectional design prevented the assessment of test–retest reliability and responsiveness to changes in dietary adherence or symptom severity. Data collection also coincided with the COVID-19 pandemic, which may have affected HRQoL and well-being and thus influenced measurement properties. The preference elicitation study covered only a limited set of health states and did not include a vignette representing asymptomatic (silent) CD, partly due to uncertainties in the evidence base on its natural history [223]. In addition, the top-down titration format used for TTO may have biased utilities upward by shaping trading behaviour, and differences in VAS format (vertical for current health vs. horizontal for hypothetical states) may also have influenced responses [91]. A limitation of the bolt-on evaluation was the limited qualitative input in the two newly developed bolt-ons (GI and DI).

5.5. Future challenges and research priorities

Despite advancements in understanding the HRQoL and well-being impact of CD and the development of preference-based evidence to support economic modeling and health care decision-making, several areas require further exploration to strengthen the methodological foundations and practical relevance of future evaluations.

First, longitudinal evidence is needed to assess temporal changes in HRQoL and capability well-being associated with diagnosis, long-term dietary adherence, symptom fluctuations and potential new treatments. Responsiveness and test–retest reliability should be established for both the EQ-5D-5L bolt-ons and the ICECAP-A to determine their suitability for repeated measures in clinical and research settings. In parallel, studies including untreated or newly diagnosed patients are necessary to better capture the full range of disease burden and to evaluate whether preference-based methods perform consistently across disease stages.

Second, future research should aim to expand the evidence base on directly elicited utilities for CD. Direct preference elicitation studies such as TTO or discrete choice experiments should be conducted in larger, population-representative samples and ideally compared with utilities derived using EQ-5D-5L.

Third, a further refinement and validation of CD-specific extensions to generic instruments would be beneficial. The promising performance of the GI and DI bolt-ons require mixed-methods confirmatory research in broader and more heterogeneous patient cohorts, across cultural contexts, and in clinical conditions with overlapping symptomatology such as gluten intolerance, IBS and IBD.

Fourth, the findings support increased attention to capability-based outcomes in CD. While ICECAP-A demonstrates promise to measure broader aspects than health in CD, future research should evaluate its applicability in assessing cost-effectiveness of new CD treatments.

Fifth, from a health policy perspective, economic studies incorporating both patient and public preferences are needed to guide reimbursement policies for GFD products and emerging therapies. The high WTP observed in our study suggests that patients may strongly prioritise reducing the burden of strict dietary adherence, an aspect that should be recognised in value-based care strategies.

Finally, with therapeutic innovation accelerating—such as enzyme therapies, immunomodulators and vaccine-based approaches—future research must ensure that outcome measurement keeps pace with clinical developments.

6. Conclusion

This thesis overall generated utility and willingness-to-pay values for relevant CD health states, examined the psychometric performance of adding bolt-on dimensions to the EQ-5D-5L, and assessed the ICECAP-A capability measure's ability to capture broader impacts of the condition. Together, these studies provide novel evidence to support more comprehensive and accurate measurement of HRQoL and well-being in individuals living with CD.

Preference elicitation study

This study provides the first TTO-based utility values in adults with CD, alongside VAS and WTP estimates for current health and GFD-related hypothetical health states. Our results show that inadequate adherence to a GFD is associated with substantial reductions in HRQoL, while strict adherence improves outcomes but does not fully remove the burden of CD. Sociodemographic and clinical characteristics contributed to variation in preferences. The resulting utility and WTP estimates can inform future economic evaluations on CD, including dietary management strategies, screening approaches, reimbursement or subsidy policies, and emerging therapeutic alternatives.

EQ-5D-5L bolt-on study

This study evaluated five EQ-5D-5L bolt-on dimensions in adults with CD and demonstrated that their inclusion reduces ceiling effects and enhances the discriminatory power of the instrument. Among them, the GI bolt-on showed the strongest psychometric performance, indicating that gastrointestinal symptoms remain an important determinant of HRQoL in CD and are not fully captured by the core EQ-5D-5L dimensions. The DI, SL, and TI bolt-ons also showed added value, particularly in reflecting the psychosocial and lifestyle consequences of strict dietary management. In contrast, the additional contribution of the CO bolt-on appeared limited in this population.

ICECAP-A psychometric testing study

This study provides the first evaluation of the psychometric performance of the ICECAP-A instrument in patients with CD. ICECAP-A demonstrated overall good measurement properties in this population. Compared to the EQ-5D-5L, ICECAP-A exhibited no

ceiling effects and showed stronger associations with the SWLS. However, the ICECAP-A was less sensitive than the EQ-5D-5L in differentiating between clinically relevant known groups. These findings suggest that ICECAP-A is a valuable tool to assess well-being of patients with CD and offers a useful complement to the EQ-5D-5L in outcome measurement.

General conclusion

This thesis contributes to the advancement of methods to assess HRQoL and well-being in CD. The results show that while the EQ-5D-5L captures important health impacts of CD, relevant bolt-ons can further improve its performance. The capability-based measure, ICECAP-A performed well in reflecting the broader burden experienced by patients. Additionally, the first TTO utilities and WTP estimates for CD health states offer valuable inputs for future economic evaluations of GFD and emerging interventions. Overall, this work supports the adoption of more sensitive and CD-relevant outcome measures to guide clinical and policy decisions and ultimately improve patient care.

7. Summary

This PhD thesis investigated HRQoL and capability well-being in individuals with CD. The work consisted of three separate but related studies based on a cross-sectional survey among 312 Hungarian adult CD patients between 2020-21.

The first study generated the first TTO-based utility values in adults with CD, alongside VAS and WTP values for current health and three hypothetical health states reflecting different levels of adherence to a GFD. Poor or absent adherence to a GFD resulted in decreases in utilities, underscoring the HRQoL burden of untreated CD. Older age at diagnosis, male gender, lower income, more severe gastrointestinal symptoms, and comorbidities were associated with worse outcomes. These results provide crucial information for future cost-utility analyses of interventions, including dietary support.

The second study examined the psychometric performance of five EQ-5D-5L bolt-on dimensions (cognition, sleep, tiredness, dining, and gastrointestinal problems) in CD. Adding bolt-ons reduced ceiling effects and improved the instrument's informativity. Among them, the gastrointestinal bolt-on demonstrated the strongest psychometric performance, highlighting the continued relevance of gastrointestinal symptoms even among patients following a GFD.

The third study provided the first psychometric assessment of ICECAP-A in CD, evaluating its ability to capture capability well-being impacts beyond health. ICECAP-A demonstrated good measurement properties with no ceiling effects and stronger associations with SWLS than EQ-5D-5L. However, EQ-5D-5L showed greater sensitivity to clinically defined differences in gastrointestinal symptom severity. These findings suggest that ICECAP-A complements generic HRQoL measures and may be valuable in evaluating social and emotional consequences of CD.

Overall, this PhD thesis contributes new utility data, demonstrates the value of EQ-5D-5L bolt-ons, and support the use of capability measures to capture the wider impacts of CD. The findings provide a methodological basis for more accurate outcome assessment and health economic evaluations in CD.

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9. Bibliography of the candidate's publications

Publications related to PhD dissertation. **Total IF: 9.7**

Angyal M Mercédesz, Lakatos Péter L, Jenei Balázs, Brodszky Valentin, Rencz Fanni: Health utilities and willingness to pay in adult patients with coeliac disease in Hungary
QUALITY OF LIFE RESEARCH 32: 9 pp. 2503-2516. (2023).
Q1, **IF: 3,3**

Angyal M Mercédesz, Janssen Mathieu F, Lakatos Péter L, Brodszky Valentin, Rencz Fanni: The added value of the cognition, dining, gastrointestinal problems, sleep and tiredness bolt-on dimensions to the EQ-5D-5L in patients with coeliac disease
EUROPEAN JOURNAL OF HEALTH ECONOMICS 26: 3 pp. 473-485. (2025)
D1, Q1, **IF: 3,0**

Angyal M Mercédesz, Pangestu Stevanus, Lakatos Péter L, Brodszky Valentin, Rencz Fanni: Psychometric testing of the ICECAP-A in patients with coeliac disease: a comparative analysis with EQ-5D-5L
HEALTH AND QUALITY OF LIFE OUTCOMES 23: 1 Paper: 112, 11 p. (2025)
Q1, **IF: 3,4**

Conference abstracts:
Angyal Mária M, Lakatos Péter L, Brodszky Valentin, Rencz Fanni: PT31 Psychometric Testing of the ICECAP-A in Patients With Coeliac Disease: A Comparative Analysis With EQ-5D-5L
VALUE IN HEALTH 28: 6 pp. 360-361. (2025)

Angyal MM, Janssen MF, Lakatos PL, Brodszky V, Rencz F: Az EQ-5D-5L egészséggel-összefüggő letminőség kérdőív „bolton" dimenziókkal kiegészítésének vizsgálata a cöliákiában
Central European Journal Of Gastroenterology and Hepatology / Gasztroenterológiai és Hepatológiai Szemle 10: Suppl. 1 p. 73-73. (2024)

Angyal M, Janssen MF, Lakatos PL, Brodszky V, Rencz F: PCR225 The Added Value of the Cognition, Dining, Gastrointestinal Problems, Sleep, and Tiredness Bolt-Ons for the EQ-5D-5L in Patients With Coeliac Disease
VALUE IN HEALTH 26: 12 p. S492-S492. (2023)

Angyal MM, Lakatos PL, Jenei B, Brodszky V, Rencz F: POSA376 Health State Utilities and Willingness to Pay in Patients with Coeliac Disease
VALUE IN HEALTH 25: Supplement 1 p. S222. (2022)

Additional conference abstract presentations:

1. Health State Utilities and Willingness to Pay in Patients with Coeliac Disease. Semmelweis Symposium; 7–9 November 2022; Semmelweis University, Budapest, Hungary.
2. Health State Utilities and Willingness to Pay in Patients with Coeliac Disease. PhD Scientific Days; 22–23 June 2023; Semmelweis University, Budapest, Hungary.
3. Az EQ-5D-5L egészség-hasznosságot értékelő kérdőív “bolt-on” dimenziókkal kiegészítésének vizsgálata a cöliákiában. Hungarian Health Economics Association Annual Conference (META); 9 October 2023; Budapest, Hungary.
4. The Added Value of the Cognition, Dining, Gastrointestinal Problems, Sleep, and Tiredness Bolt-Ons for the EQ-5D-5L in Patients with Coeliac Disease. Semmelweis Symposium; 11–13 December 2023; Semmelweis University, Budapest, Hungary.
5. The Added Value of the Cognition, Dining, Gastrointestinal Problems, Sleep, and Tiredness Bolt-Ons for the EQ-5D-5L in Patients with Coeliac Disease. PhD Scientific Days; 9–10 June 2024; Semmelweis University, Budapest, Hungary.
6. The Added Value of the Cognition, Dining, Gastrointestinal Problems, Sleep, and Tiredness Bolt-Ons for the EQ-5D-5L in Patients with Coeliac Disease. Lifestyle Medicine Conference; 10–12 October 2024; Hévíz, Hungary.
7. Az ICECAP-A kérdőív pszichometriai tulajdonságai és összehasonlító elemzése az EQ-5D-5L kérdőívvel cöliákiás betegek jóllétének értékelésében. Lifestyle Medicine Conference; 9–11 October 2025; Mezőkövesd, Hungary.

8. The Added Value of the Cognition, Dining, Gastrointestinal Problems, Sleep, and Tiredness Bolt-Ons for the EQ-5D-5L in Patients with Coeliac Disease. Semmelweis Symposium; 11–13 November 2024; Semmelweis University, Budapest, Hungary.
9. The Added Value of the Cognition, Dining, Gastrointestinal Problems, Sleep, and Tiredness Bolt-Ons for the EQ-5D-5L in Patients with Coeliac Disease. Association of European Coeliac Societies (AOECS) Annual Conference; 14–17 November 2024; Madrid, Spain.
10. Psychometric Testing of the ICECAP-A in Patients with Coeliac Disease: A Comparative Analysis with EQ-5D-5L. PhD Scientific Days; 7–9 July 2025; Semmelweis University, Budapest, Hungary.
11. Az ICECAP-A kérdőív pszichometriai tulajdonságai és összehasonlító elemzése az EQ-5D-5L kérőívvel cöliákiás betegek jóllétének értékelésében. Hungarian Health Economics Association Annual Conference (META); 13 October 2025; Budapest, Hungary.
12. Psychometric Testing of the ICECAP-A in Patients with Coeliac Disease: A Comparative Analysis with EQ-5D-5L. Association of European Coeliac Societies (AOECS) Annual Conference; 17–18 October 2025; Brussels, Belgium.

Scientific meeting presentation:
Scientific Meeting on Coeliac Disease International Day. Hungarian Health Economics Association (META); 20 May 2025; Budapest, Hungary.

Conference moderation:
Outcome Measurement and Valuation in Health and Well-being — Session Moderator. 2025 International Health Economics Association Congress (iHEA); 21 July 2025; Bali International Convention Centre, Bali, Indonesia.

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