# THE ROLE OF THE COST OF DISEASES AND QUALITY OF LIFE IN THE ALLOCATION OF HEALTHCARE RESOURCES

## PH. D. THESIS

Supervisors: Prof. Márta Péntek, Prof. László Gulácsi Dsc

## Zsuzsanna Beretzky

Budapest, 2020

# ZSUZSANNA BERETZKY

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# TABBLE OF CONTENTS

# LIST OF FIGURES

# LIST OF TABLES

## LIST OFABBRIVIATIONS

| | |
|---|---|
| AMD | age-related macular degeneration |
| AP | psoriatic arthritis |
| BC | bladder cancer |
| BPH | benign prostatic hyperplasia |
| BIA | Budget Impact Analysis |
| BNO | betegségek nemzetközi osztályozása |
| CEA | Cost Effectiveness Analysis |
| COI | Cost of Illness |
| CUA | Cost-Utility Analysis |
| DB | disease burden |
| DCE | discrete choice experiment |
| DLQI | Dermatology Life Quality Index |
| EHIS | European Health Interview Survey |
| EMMI | Ministry of Human Resources (Emberi Erőforrások Minisztériuma) |
| EQ-5D-5L | The 5-level EuroQoL Group's 5-dimensions questionnaire |
| EQ-5D-3L | The 3-level EuroQoL Group's 5-dimensions questionnaire |
| EUnetHTA | European Network for Health Technology Assesment |
| GALI | Global Activity Limitation Indicator |
| HBCS | The Hungarian version of DRG (Homogén betegségcsoportok) |
| HTA | health technology assessment |
| ICECAP-A | ICEpop CAPability measure for Adults |
| ICECAP-O | ICEpop CAPability measure for Older people |
| ICD-10 | International Statistical Classification of Diseases and Related Health Problems 10th Revision |
| ICER | incremental cost-effectiveness ratio |

| | |
|---|---|
| MEHM | Minimum European Health Module |
| NHIFA | National Health Inscurance Fund Manager (Administration) |
| OAB | overactive bladder |
| PASI | Psoriasis Area Severity Index |
| PRISMA | Preferred Reporting Items for Systematic Reviews and Meta-Analyses |
| RA | rheumatoid arthritis |
| RUD | Resource Utilization in Dementia |
| QALY | Quality-Adjusted Life Year |
| QoL | Quality of Life |
| SF-36 | Short Form (36) Health Survey |
| SG | standard gamble |
| SM | multiple scleorsis |
| SSc | systemic sclerosis |
| TTO | Time Trade-Off |
| VAS | Visual Analogue Scale |
| WHO-5 | World Health Organisation- Five Well-Being Index |

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## 1. INTRODUCTION

Healthcare cost are increasing and are already very high worldwide and in Hungary. In Hungary, per capita health expenditure is below the EU average. In Hungary, per capita health expenditure was 1996 USD in 2017, in the same year it was 5848 USDin Germany, 5264 USD in Sweden, and 5025 USD in Denmark. (OECD, 2020). Hungary spent 7.4% of its GDP on health care, which was also below the EU average of 9.9% (EurópaiBizottság, 2017, Eurostat, 2019).

The economics of chronic diseases are issues of great importance from the point of view of health policy and financing, as these diseases cause significant burden not only for the individual, the family, but on a societal level too.

Healthcare needs are similar to that of high-income countries. In Hungary, life expectancy was 76.2 years in 2018, healthy life expectancy was 61.1 years, while life expectancy in Germany was 81.0 years, and in Austria 81.8 years. Healthy life expectancy was 65.8 years 56,9 years in 2018 (Eurostat, 2018b, Eurostat, 2018a).

Knowledge of costs and outcomes (disease, disease burden), analysis of the cost-effectiveness of therapies is essential information for the financier and health policy-maker in order to achieve sustainable financing in health care sector and create the optimal allocation of resources.

The identification and measurement of different costs in chronic diseases, as well as the analysis of outcomes including the quality of life of patients (and family members, carers), contributes significantly to the disease burden assessment in financing decisions. In Hungary, such data are not available from the databases of the financier, the National Health Insurance Fund Management (NHIFA).

The importance of health economics analysis, similarly to other developed countries, is growing in Hungary. This is due to the fact that an increasing part of the health care budget is allocated, in accordance with legal requirements, taking into account the results of health economics analysis (EMMI, 2017, Gulácsi et al., 2014b).

The economics of chronic diseases is an extremely important issue from the point of view of health policy, public health resource allocation and financing, as the disease burden and costs are significant and constantly increasing not only at the individual, family, but also on a societal level. Information on costs and outcomes, analysis of the cost-effectiveness of therapies is essential information for the financier and health policy decision-maker in order to achieve sustainable financing in healthcare sector.

The identification and measurement of different costs for each chronic disease, as well as the analysis of non-therapeutic and non-therapeutic outcomes, including the quality of life of patients (and family members, carers), contributes significantly to the disease burden assessment. In Hungary, such data are not available from the databases of the financier, formerly the National Health Insurance Fund, currently the National Health Insurance Fund Manager (NHIFA).

The importance of health economics analysis, like in other developed countries, is large and constantly growing in Hungary. The reason for this is that an increasing part of the health care budget is allocated in accordance with legal requirements, also taking into account the results of health economics analysis (Gulácsi et al., 2014b). The most important methods are costing, disease burden, cost-effectiveness and budgetary impact analyses.

These calculations require valid, standardized, periodically updated, and available cost data (unit costs) and outcome information. It is very important that in the course of analyses and health economics calculations, these data are used in the same way in all cases, regardless of whether they are made in the competitive or public sector (pharmaceutical distributors or AEK), as the results are only in this case. can be compared.

In the case of health resource allocation decisions, budgetary effects and cost-effectiveness results are compared, benefit-sacrifice costs are examined, and accordingly, the usability of the data without meeting the comparability requirements is severely limited.

Examples of such unit costs are the cost of one GP visit, the cost of an ambulance service for 1 km, the cost of 1 hour of informal care, the cost of an average hospital admission, the cost of being absent from work and the productivity loss during work due to illness. Cost-effectiveness calculations often require knowledge of costs associated with a disease

that can be avoided in whole or in part as a result of the use of a particular drug. For this, it is necessary to know, for example, the costs of stroke, myocardial infarction, rheumatoid arthritis and other diseases in Hungary.

The lack of a database summarizing costs and unit costs for a given country (called the Hungarian cost library) as we can see in Hungary, makes it very difficult to standardize cost calculation methods and contributes to different unit costs in different analysis. Often it is not even possible to clearly state which unit costs were used for the cost calculation and the health economics analysis. Because of this, the validity of the results is unknown and comparability is very uncertain.

One important area is the inclusion (into financing) of new therapies in the social insurance system, during which it is absolutely important to assess the costs of the given health technology (prevention, screening, diagnosis, therapy) and the potential benefits of its use.

Conducting cost-effectiveness and budget impact analysis prior to health policy and financing decisions is required by all European (and other developed countries) legislation. Mandatory consideration of cost-effectiveness aspects in health policy decisions is also regulated in a decree in Hungary (7/2016. (III. 30.) EMMI rendelet) „a biztonságos és gazdaságos gyógyszer- és gyógyászatisegédeszköz-ellátás, valamint a gyógyszerforgalmazás általános szabályairól" (EMMI, 2017). Local cost data must be used  for the analysis, as cost data from other countries cannot be transferred to Hungary, due to very significant differences in unit costs, health financing and healthcare practices. (Brodszky et al., 2019).

Cost-of-illness (COI) studies provides information on the economic burden of a particular disease, from an individual, financial, or societal perspective. Their aim is not only to identify the costs associated with the disease, but also to determine the overall societal burden, including healthcare and non-healthcare costs, thus helping to understand the significance of a given health problem and identify key cost items and cost structure (Drummond et al., 2005). As a result, cost of illness studiesare extremely important and contribute to supporting decision-making processes (Boncz et al., 2006). The growing role of HTA in the countries of the region over the last decade makes it even more necessary to use reliable, local (country-specific) cost data (Gulácsi et al., 2014b, Feig et al., 2017, Boncz et al., 2006).

There is no golden standard for conductiong costing and cost of ilness analysis (Larg et al., 2011, Jacobs et al., 2005, Raspe et al., 1998). Alongside to the harmonization of different methodologies, it is becoming an increasingly important aim to establish comparability; currently, different research in many cases uses different structures, methodologies, perspectives, and costing approaches (Angelis et al., 2015, Onukwugha et al., 2016).

In the case of chronic diseases, not only the presence of direct health care costs, but also the direct non-health care and the indirect costs can cause significant burden on a societal level. Previous studies show that in many chronic diseases, informal care is a major factor inn patient care. In addition to current demographic trends, the use of informal care is expected to become an increasingly common. Informal care is the care provided to patients and those in need, outside the formal, state-funded framework of health care and social care, which is not reimbursed. Patients receive help from family members, those living in the same household as them and friends to carry out their daily tasks (dressing, bathing, eating, housework), informal helpers shop, buy prescription medications, and arrange other matters, and take the patient to health care facilities if needed. Even on acute conditions, the help provided by family members may become necessary (childbirth, postoperative periods), but in chronic diseases, long-term informal assistance may be even more important. Informal care takes a lot of time of the helpers (informal caregivers) and many of them drop out or miss work, which is why informal care is becoming an increasingly important field nowadays (Gulácsi et al., 2012, Beretzky et al., 2017, Zemplenyi et al., 2016). In addition, informal care can have a negative impact on the health and quality of life of informal carers and can lead to significant costs (Krol et al., 2015). The time spent on informal care and the associated costs can be considered as a disease-related cost, assuming that in its' absence it would be necessary to replace this care activity with formal health and social care.

However, informal care can in many cases be underestimated if its costs are ignored in the economic evaluation of health interventions (Krol et al., 2015), therefore, the inclusion of informal care in health economics analysis of chronic diseases can influence their outcomes and contribute to better decision-making in policy-making (van den Berg et al., 2004). Access to informal care depends on a number of factors, such as the socio-demographic attributes of the society, so in addition to knowing country-specific data, we get a more comprehensive picture of the burden of disease.

In chronic illnesses that last for decades, informal care is even more important. This has an important role to play in aging societies, as life expectancy has increased and is increasing significantly, as people live longer and longer with more or less reduced self-sufficiency and therefore need the help of others temporarily or permanently (Verbakel et al., 2017), In 2015, the proportion of people over the age of 65 among the population of the EU28 Member States was 18.9%, while in Hungary it was 17.9% (Eurostat, 2017). The aging of the "baby-boomer" age groups also significantly increases care needs.

However, the need for informal care is not limited to the elderly. An increasing number of children and young adults are living with severe chronic illness and require informal care. Examples are the so-called rare diseases, in which the number of patients in each disease is not high, but hundreds of thousands of patients are affected by more than a thousand different rare diseases (Cavazza et al., 2016b, Kuhlmann et al., 2016, Iskrov et al., 2016, Lopez-Bastida et al., 2016a, Péntek et al., 2016c, Cavazza et al., 2016a). As a result of the use of increasingly effective medical technologies, the life expectancy and number of people living with chronic diseases in developed countries, including Hungary, will increase significantly. This trend is also well observed in European countries, where the incidence of activity-limiting chronic diseases has increased significantly. These include dementia, osteoporosis, cardiovascular disease and cancer.

Nowadays, the cost of informal care for people with chronic illnesses is significant, in most cases it exceeds the direct health care costs. (Hoefman et al., 2013, Eurostat). These costs have been in exceeded of the costs of the insurance and state-funded health care sectors in the United States decades ago. (Arno et al., 1999). Informal care can to some extent replace insurance or state-funded health / social care, thereby reducing these health care expenditures (Bremer et al., 2015, Boncz et al., 2006). However, it is also an important aspect that the health of informal carers sometimes deteriorates and their ability to work decreases (Colombo et al., 2011). With the current demographic trends continuing, it is predictable that the need for informal care and the resulting costs will continue to increase significantly (Vlachantoni et al., 2013, KSH, 2013).

The burden of chronic diseases is increasing, as these conditions are the main causes of health and health-related quality of life decline, and a significant part of health expenditure is also attributable to them (Bauer et al., 2014). Measuring health-related quality of life in chronic diseases helps to assess the effectiveness of a given therapy and

provides information on potential health gains. This information can help optimize resource allocation and help decision-making.

Quality of life is a multidimensional concept which includes of health-related quality of life. There are a number of diseases that do not significantly affect life expectancy but have a negative impact on a patient's quality of life. Therapies for the treatment of diseases also have an impact on quality of life in many cases, and without measuring this, their real benefits cannot be estimated. Measuring health-related quality of life contributes to the identification of needs, the description of health conditions, and helps, to make choices between different therapies, thereby contributing to the efficiency of resource allocation. Nowadays, measuring the quality of life is becoming more and more important, as more and more people live with chronic diseases for a longer period of time, which is why public health programs are paying more and more attention to the quality of life.

The field of research is of key public policy importance. Within a country, groups of the population with different demographic and socio-economic characteristics have different health needs and may receive different health care, the assessment of which is a significant issue.

Stiglitz highlights the importance of state intervention in health care. Health policies aim to develop a health system that is health-oriented, seeks to influence socio-economic and health determinants of health, provides equal opportunities, is effective, can be financed, and seeks to maximize health status with the limited resources available (Stiglitz, 2000).

In the field of healthcare, a number of market failures are emerging, the presence of which also justifies the need for public intervention: the problem of public goods, externalities, information asymmetries, limited competition and the meritorical nature of goods (Stiglitz, 2000).

Information asymmetries are significant in the field of health care, and health care recipients must rely on the knowledge and decisions of the physician and other health care professionals. However, the physician does not have complete information in all areas, for example, they are aware of the results of the patient's laboratory tests, but does

not necessarily know the patient's general health, quality of life, well-being or their impact on social abilities.

Reducing information asymmetries is also hampered by the difficulty of comparing services (cost, quality, efficiency). In the healthcare sector, this comparison is not feasible, as there are too many different interventions, hospitals and doctors present, for example, a hospital may be excellent in performing certain interventions and weak in others (Stiglitz, 2000).

The need to reduce information asymmetry makes it difficult to compare services (cost, quality, efficiency). In the healthy sector, this comparison is not applicable, as there are too many different interventions, the presence of a hospital and a doctor, in one hospital it is necessary to perform excellence in performing it, in another intervention it may be weak.

In addition, competition between hospitals is limited, and good and efficient providers are not expected to crowd out the weaker ones to gain a competitive advantage. In most towns, even large ones, there is only one hospital (Stiglitz, 2000). „The patient relies on the doctor's judgment as to what medication to take, whether it is advisable to undergo surgery, and so on" (Stiglitz, 2000, p315.).

As Stiglitz puts it, "Incomplete information reduces the effective level of competition". "At the same time, the heterogeneity of medical services makes price and quality comparisons very difficult, and therefore not conducive to the effective dissemination of information." (Stiglitz, 2000, p316.) and "The practice of the medical profession is probably consistent with the fact that competition is inevitably limited due to imperfect information." (Stiglitz, 2000, p316.). Stiglitzs also highlighted that „Most hospitals are non-profit institutions" (Stiglitz, 2000, p316.).

Today, this is why governments and insurers try to measure not only this (quality, cost), but also the condition of the patient at the time of admission and discharge (by generic and disease-specific measures).

Increasingly, funders do not want to "buy" health services but "results," which can be expressed as health gains.

Decision-making is partly the job of doctors and health-care professionals, but they also have to account for health gains. In part, the decision is made by the financier of a given country, by determining what to finance.

It is noteworthy that excessive health care spending can be inadequate and can cause harm. The results of one study showed that the probability that a child's tonsils were removed ranged from 7 to 70% in Vermont, USA. This phenomenon, called over-management, is also characteristic of Hungary, one of the consequences of information asymmetry, which the OECD has repeatedly pointed out in its country report (OECD, 2019).

The two most significant elements of health financing are resource creation and resource allocation, i.e. the mechanisms and methods through which resources are used (Stiglitz, 2000). In the existence of a publicly funded care system, a significant question is how health services are financed by the state, i.e. the 'public', and its members, who maintain the health care system through their contributions.

At the moment, in Hungary, short-term and long-term public funding decisions related to health care are not routinely collected and data of adequate quality and quantity are not available.

The dissertation reports on the results of different health economics researches, accordingly it is characterized by significant methodological heterogeneity, as different researches often require the application of very different methodologies.

The structure of the dissertation is as follows:

Starting from Chapter 4 of the dissertation, the member in the second position (local value) of the numbering in each chapter indicates the description of a larger research circle. Accordingly, starting in Chapter 4, subsections 4.1, 5.1, 6.1, and 7.1 present the objectives, methodology, results, and discussions of the same research.

"1." in the second position of the chapter numbering marked subsections discuss research on quality of life measurement. The subchapters, denoted by a number with a third local value, denote individual researches in the field of quality of life measurement.

Comparison of four different EQ-5D-3L value sets (1)[1] (Zrubka et al., 2019), a detailed analysis of the DLQI questionnaire (2)[2] (Rencz et al., 2018),  the anlysis of the health state and productivity of the Hungarian general population (3) (Péntek et al., 2020)[3], and the characteristics and determinants of informal care (4) (Beretzky et al., 2017)[4].

In the second position of the chapter numbering "2." the topic of the marked subchapters is costing in health care; this sub-chapter also includes further research, which has been separated by numbers in the third local value of the chapter numbering: measuring the costs of informal care (1) (Beretzky)[5], cost of illness studies in the Central Eastern European region (2) (Brodszky et al., 2019)[6], and the Hungarian cost library (3).

The structure of the dissertation is displayed on Figure 1. (Figure 1.)

[1] The corresponding subsections are based on the following publication: Zrubka Zs, **Beretzky Zs**, Hermann Z, Brodszky V, Gulácsi, L, Rencz, F, Baji P, Golicki D, Prevolnik-Rupel V, Péntek M (2019): A comparison of European, Polish, Slovenian and British EQ-5D-3L value sets using a Hungarian sample of 18 chronic diseases. European Journal of Health Economics 20, Suppl. 1, pp. 119-132.

[2] The corresponding subsections are based on the following publication: Rencz F, Poór AK, Péntek M, Holló P, Kárpáti S, Gulácsi L, Szegedi A, Reményik É, Hidvégi B, Herszényi K, Jókai H, **Beretzky Zs**, Brodszky V (2018): A detailed analysis of 'not relevant' responses on the DLQI in psoriasis: potential biases in treatment decisions. Journal of The European Academy of Dermatology and Venereology, 32, 5, pp. 783-790.

[3] The corresponding subsections are based on the following publication: Péntek M, **Beretzky Zs,** Brodszky V, Szabó, A. Kovács, L. Kincses, Á. Baji P, Zrubka Zs, Rencz F, Gulácsi L: A magyarországi lakosság egészséggel összefüggő munkaképessége: keresztmetszeti reprezentatív felmérés a Munkaképességre és Tevékenységcsökkenésre vonatkozó kérdőívvel. Orvosi Hetilap, accepted for publication

[4] The corresponding subsections are based on the following publication: **Beretzky Zs,** Péntek M (2017): Informális ellátás és meghatározó tényezői krónikus betegségekben: magyarországi kutatások összehasonlító elemzése [Characteristics and determinants of informal care in chronic diseases in Hungary: a comparative analysis] Orvosi Hetilap, 158, 52, pp. 2068-2078.

[5] The corresponding subsections are based on the following publication: **Beretzky Zs**: Az informális ellátás költsége krónikus betegségekben: magyarországi kutatások összehasonlító elemzése. Köz-Gazdaság, accepted for publication

[6] The corresponding subsections are based on the following publication: Brodszky V, **Beretzky Zs**, Baji P, Rencz F, Péntek M, Rotar A, Tachkov K, Mayer S, Simon J, Niewada M, Hren R, Gulácsi L (2019): Cost-of-illness studies in nine Central and Eastern European countries. In: European Journal of Health Economics, 20, Suppl1, pp. 155-172.

**Figure 1. The structure of the research topics presented in the thesis**

Public policy

Government

Healthcare sector

Budget Impact Analysis

Costs

Direct costs

Cost-of-illness studies in nine Central and Eastern European countries

Hungarian cost library

Indirct costs

Absenteeism

Presenteeis m

Individual and societal benefits

HRQoL

Disease-specific

DLQI

Generic

EQ-5D, ICECAP

A detailed analysis of 'not relevant' responses on the DLQI in psoriasis

A Comparison of European Polish, Slovenian and British EQ-5D-3L value sets using a Hungarian sample of 18 chronic diseases

Work productivity

WPAI

The health state and productivity of the Hungarian general population

Societal burden

Informal care

Characteristics and determinants of informal care in chronic diseases in Hungary

Cost of informal care in chronic diseases in Hungary

## 2. BACKGROUND

In this chapter, I summarize the most important theoretical concepts and methodological background of the research applied and planned in the dissertation.

In our research, we examined the reduction in quality of life and costs caused by diseases, as well as the health gains (disease-specific and generic measures), cost-effectiveness, and budgetary impact of therapies. Decreased quality of life (and its consequences, social impact) is the burden of disease caused by the disease, which can be at least partially avoided by using appropriate therapies. Together, these are necessary for health economics analysis. As different theoretical concepts and methodologies have been applied, this may also appear to be a methodological heterogeneity, although the full range is required for the studies. The following section presents the background of these studies and the methodological concepts used in this thesis.

### 2.1. Health-related quality of life

In addition to life expectancy, quality of life is the most important indicator in evaluating the consequences of diseases and the benefits of therapies. Quality of life is influenced by a number of factors, in this case we focus on discussing and researching health-related quality of life related.

General and disease-specific measures are used to measure health-related quality of life.

The most widely used generic quality of life measure in most languages in the world is the EQ-5D questionnaire and a disease-specific quality of life questionnaire used in the field of dermatology: the Dermatological Quality of Life Index (DLQI).

Generic measures enable comparison of changes in quality of life between different diseases and to calculate cost-effectiveness as described in this chapter, so the results are also useful for health policy decision makers.

Disease-specific measures are suitable for measuring disease severity and monitoring the effect of therapy, and are accordingly used in clinical practice. The results of these measures are used to determine the indication for (often very costly) therapies (when the patient can receive therapy). Therefore, these medical decisions are also resource allocation decisions (since the doctor makes public vouchers from the social security fund with the indication decisions), so they are also of great economic importance.

### 2.1.1. The EQ-5D questionnaire

The most commonly used questionnaire to measure health-related quality of life is the EQ-5D questionnaire (Brazier et al., 2019). The descriptive system focuses on five dimensions of health: Mobility, Self-care Usual activities, Pain/discomfort and Anxiety/depression. In each dimension, there are three categories that respiondents can choose from, representing: no problems - 1, moderate problems 2; severe problems- 3. Respondents are asked to indicate for each dimension the level of problem that best describes their current health status. The '21112' EQ-5D profil signifies a health stat with moderate problems in Mobility and Anxiety/depression. (EuroQolGroup, 1990). The EQ-5D-5L version has 5 choices for the fivre different level of problems, resulting in 3125 ($3^7$) different health staes (Herdman et al., 2011). The EQ-5D questionnaire includes a visusal analogue scale, the so-called EQ VAS, where respondents can indicate their current health state beetween 0 (worst imagineable health state) and 100 (complete health). To each EQ-5D a utility value can be attached. EQ-5D-3L value sets have been developed in many different countries, and are based on preferences of the general population, they were created using direct methods such as time trade-off, visual analogue scale, standard gamble, SG), or discrete choice experiment.  The country specific value sets reflect the characterics of the

given country and the preferences of the general population. Previous studies suggest that the differences are attributable to socio-demographic and cultural factors (Devlin et al., 2017). The studies presented here in this thesis used the UK (United Kingdom) EQ-5d value set, as a Hungarian value set was not available at the time of the research (Baji et al., 2015). The Department of Health Economics used the EQ-5D questionnaire in a number of previous studies (Péntek et al., 2014, Pentek et al., 2013, Péntek et al., 2012c, Péntek et al., 2012a, Péntek et al., 2016c, Péntek et al., 2007, Rencz et al., 2014, Rencz et al., 2015c, Balogh et al., 2013, Bernert et al., 2009, Brodszky et al., 2009, Brodszky et al., 2010d, Batog et al., 2018).

### 2.1.2. Utility

In health economic analysis utility is used to measure the preference for a specific health condition or outcome. The utility of total health is considered to be 1, and the utility value of 0 can be associated with the state of death. "Worse than death" conditions have a negative utility value. Utility can be measured using direct and indirect methods. Direct methods are standard game (SG), visual analog scale (VAS) and time trade-off (TTO). The tools of indirect utility measurement are e.g. EQ-5D or the Short-Form 6D (SF-6D) questionnaire.

### 2.1.3. Disease specific questionnaires: Dermatology Life Quality Index

Quality of life can be measured not only with general but also with disease-specific questionnaires. The Dermatology Life Quality Index (DLQI) questionnaire has 10 items and respondents can choose answers corresponding with a score between 0 and 3 for each question, depending on how much the skin problem affected the patient's quality of life in the week before completion (Basra et al., 2008). The 10-item questionnaire covers six areas of health-related quality of life: symptoms, daily activities, leisure, work and education, personal relationships, and treatment. Each question was scored on a four-point scale (0 =

"not at all", 1 = "slightly", 2 = "fairly", 3 = "very much"). In addition, for eight questions, the respondent has the option to indicate a "not relevant response" (NRR) answer, which has a value of 0, similar to the "not at all" answers. The total score of each element can be between 0 and 30, where a higher value can be associated with a greater deterioration in quality of life (Basra et al., 2008).

The NRR response option appears in 80% of the questions, which is unusual for a short questionnaire, however, their examination is rare and inconsistent in the literature. The majority of DLQI studies do not report the incidence of NRR responses, however, studies from several countries have reported a large number or almost no NRR responses (Ferraz et al., 2006, Hahn et al., 2001, Herédi et al., 2014).

### 2.1.4. The concept of quality adjusted life years

One of the most commonly used measure of health outcomes, the Quality Adjusted Life Year (QALY) (Rios-Diaz et al., 2016). QALY expresses both length of life and quality of life with a value of utility. The state of perfect health is denoted by 1 and the state of death by 0.

Health conditions considered worse than death are described by negative numbers. The QALY does not differentiate between the severity of each condition or the differences in the individuals studied and does not differentiate between length of life and quality of life.

A year spent in complete health is considered equivalent to ten years in a state of 0.1 quality. If we want to express an improvement in health, we can observe that, for example, from 0.3 to 0.5 at the age of 30, and from 0.8 to 1.0 at the age of 60 (Gulácsi et al., 2012).

Utility values are assigned to each health condition by measured population preferences. These utility values are determined by the population or groups of patients based on imagined or experienced health conditions (Brazier et al., 2018).

Health-related utility can be measured by both direct and indirect methods. Direct methods measure utility by evaluating specific disease descriptions, and indirect

methods by evaluating conditions that can be described by general quality of life questionnaires. What the two methods have in common is that it evaluates the utility of a particular state with a particular utility value (Brazier et al., 2019).

### 2.1.5. Health state and well-being

In addition to quality of life measures, the health and well-being of a given patient can be measured in a number of other ways. The questionnaires and methods that were included in our research are briefly presented below.

#### 2.1.5.1. Minimum European Health Module (MEHM)

The Minimum European Health Module (MEHM) consists of three general questions. The respondent rates the present health on a five-point scale (Very good / Good /Fair / Bad / Very bad). It states whether you have a chronic illness for at least 6 months (Yes / No) and whether you have a health problem for at least 6 months (severely limited / limited, but not severely / not limited), the latter measure being the so-called Global Activity Limitation Indicator (GALI) (Eurostat, 2013, Eurostat, 2019).

#### 2.1.5.2. ICECAP-A and ICECAP-O questionnaires

The ICECAP-A (ICEpop CAPability measure for Adults) and ICECAP-O (ICEpop CAPability measure for Older People) are tools for measuring skills and experienced well-being. The standards have been developed based on Amartya Sen's approach, which bases the well-being of individuals on their ability to perform activities that are important in their lives. Both questionnaires can be used as a yardstick in health economics analyses. The ICECAP uses a broader interpretation of well-being and does not focus only on the health dimension. The ICECAP-A questionnaire focuses on five main areas: **Attachment** (an ability to have love, friendship and support), **Stability** (an ability to feel settled and secure), **Achievement** (an ability to achieve and progress in life), **Enjoyment** (an ability

to experience enjoyment and pleasure), and **Autonomy** (an ability to be independent). By completing the questionnaire, the respondent can choose from the four possible answers the statement that best describes his situation. ICECAP-O allows respondents to choose between the four answers in the dimensions Attachment (love and friendship), Security (thinking about the future without concern), Role (doing things that make you feel valued), Enjoyment (enjoyment and pleasure) and Control (independence). The ICECAP score can range from 0 to 1, with a scale of 0 indicating a complete lack of skills (Al-Janabi et al., 2012) (Flynn et al., 2015, Al-Janabi et al., 2013).

## 2.2. Costing

Assessing the burden of disease, determining the costs of diseases and health care, identifying relevant resources, measuring their use, and determining their value are the basis for costing. A significant choice in costing is the choice of perspective. The identification and measurement of data on the disease burden, disease cost, and cost of therapies for each disease is of paramount importance today, as it provides input data for health economics analyses. In order to make optimal health policy decisions and allocate resources and strive for sustainable financing, it is necessary to know detailed, country-specific cost data on the costs of individual diseases and therapies. Costs can be classified into direct health care, direct non-health care and indirect cost.

### 2.2.1. Direct healthcare costs

Resources which are directly necessary in providing healthcare services.

### 2.2.2. Direct non-healthcare costs

The direct non-healthcare costs include the cost of informal care, cost of travelling to receive health care services or remodelling of the patient's apartment due to changed needs.

#### 2.2.2.1. Informal care

Informal care is care provided by non-professional caregivers, outside of the organized health insurance founded healthcare system. Informal care is not paid, but can amount to significant burden in chronic conditions. The informal care need is quite significant in certain chronic diseases; it can amount to a large percentage of the overall cost. Previous studies show that patients suffering from Parkinson's disease or dementia require more than 12 hours of informal care weekly (Zrubka, 2017, Beretzky et al., 2017). The role of informal care is ever increasing as formal healthcare is not aiming to provide long term care for patients. (Zrubka, 2017, Beretzky et al., 2017), and patients also prefer care provided in their own home by relatives in many cases.

The cost of informal can be estimated with several different methods. Most commonly used is the market price and the opportunity cost methods. The former uses the market price of such service, the latter uses the wage of the informal carer that could be realized if the carer would do payed work in instead of providing informal care (Zrubka, 2017, Beretzky et al., 2017, Gulácsi et al., 2012).

### 2.2.3. Indirect cost

Indirect cost includes the cost of the patients' time and productivity losses experienced by the patient. Missing time from payed work or experiencing lower productivity while working is mainly measure by two methods: the human capital and the friction cost methods.

Absenteeism

Absenteeism expresses a loss of labour productivity due to absence from work due to health reasons (sick pay, long-term absence due to illness, disability).

Presenteeism

Decreased productivity may occur not only due to absence from work, but also due to decreased productivity at work due to illness, as expressed by presenteeism.

2.2.3.1.    Measuring productivity loss): Work Productivity and Activity Impairment (WPAI) questionnaire

Productivity costs can be measured using an internationally validated standardized questionnaire. The Work Productivity and Activity Impairment - General Health (WPAI-GH, "WPAI") is a questionnaire designed to assess disability due to health problems (physical and mental problems or symptoms) in paid and unpaid work. The questionnaire is suitable for measuring both absenteeism and presenteeism, as well as its barriers to unpaid work and other activities.

The questionnaire consists of six questions. Respondents must first indicate whether they are currently doing paid work (Q1). The following section (Q2-Q5) is only relevant for participants who do paid work. The number of hours absent from work due to health (Q2) and other reasons (Q3) is asked. Respondents should then indicate how many hours they actually worked in the last seven days (Q4). The rate of loss of labour productivity experienced at work is measured by the questionnaire on an 11-point scale (0: not affected, 10: completely prevented). The last question (Q6) concerns the extent to which the respondent's health problems affected his or her daily activities. This question also uses an 11-point rating scale (0: not affected, 10: completely prevented).

During the scoring, by calculating 100 times the values, they are expressed as a percentage:

**Abstenteeism:** Absence from work due to health condition: $Q2/(Q2+Q4)$

**Presenteeism:** Decreased productivity due to health status at work: $Q5/10$

**Total productivity loss while working (%):** Total labour productivity loss due to health:

$$Q2/(Q2+Q4)+[(1-(Q2/(Q2+Q4))) \times (Q5/10)]$$

**Productivity loss in other activities (%):** Decrease in productivity due to health status experienced in everyday activities: $Q6/10$

WPAI values are expressed as a percentage, where higher values indicate greater limitation and loss of productivity (Reilly et al., 2004, Reilly-Associates, 2019).

### 2.2.4. The role of Health Technology Assessment

In Hungary, several legal acts provide for aspects to be taken into account in healthcare: the role of efficiency, economy and cost-effectiveness (1993. évi költségvetéséről szóló törvény, 1992. évi LXXXIV. törvény, 1997. évi LXXXIII. törvény) (Kobelt et al., 2017). Health Technology Assessment (HTA) regulation in Hungary dates back to 2002, when the first professional directive on health technology assessment was published in Hungary, this directive was first updated in 2013 (Kobelt et al., 2017).

The Hungarian HTA guideline, the „Emberi Erőforrások Minisztériuma szakmai irányelve az egészségügyi technológia értékelés módszertanáról és ennek keretében költséghatékonysági elemzések készítéséről" (2017. EüK. 3. szám közlemény) covers the most important chapters: the need to present the given technology, the description of the curative-preventive technologies to be compared, the choice of perspective, the type of health economic analysis, the measurement of health benefits related to the applied procedures, cost calculation, time horizon of analysis, discounting and detailed presentation of results, Budget Impact Analysis and other aspects (Kobelt et al., 2017).

The main goal is to prepare funding decisions and assess the costs and benefits of a given health technology (prevention, screening, diagnosis, therapy) when including new therapies in the social security system. In Hungary, too, legislation requires the need to continue cost-effectiveness and budget-impact studies prior to making health policy and funding decisions (EMMI Decree 7/2016 (III. 30.)).

The European Network for Health Technology Assessment (EUnetHTA) defines health technology assessment as "summarizing available medical, social, economic and ethical information on the use of health technologies in a transparent, impartial and robust manner". Its main objective is to support "the most valuable, patient-centered, safe and effective health interventions possible" (EUnetHTA, 2007). The HTA modules recommended by EUHTA can be divided into the following (EUnetHTA): relative efficacy analysis (current application of the technology, technical characteristics, safety, clinical efficacy) and local evaluation (cost and economic evaluation, ethical evaluation, organizational impacts, patient-level and social effects, legal effects) (EUnetHTA, 2007).

Health economics assessment most often includes the following analyses: cost-benefit analysis and budget impact analysis. In these analyses, the given new technology is compared with a technology that is already generally accepted and used. Cost-Utility Analysis (CUA) contrasts health outcomes measured in Quality Adjusted Life Years (QALYs) with costs. Budget Impact Analysis (BIA) focuses on the financial implications of introducing a particular new technology (Gulácsi et al., 2012).

### 2.2.5. Hungarian cost library

There are 'cost-libraries' in four countries in Europe: the UK, the Netherlands, Germany and Austria. Partially, such data are available at regional, autonomous provincial level in Spain, Italy, and Sweden.

Among the countries in our region, Austria has its own 'cost-library'. The purpose of the 'cost-library', developed and managed by the Department of Health

Economics, Center for Public Health, Medical University of Vienna, is to communicate available unit costs as well as its various sources of unit costs.

The creation of the Hungarian online health care cost catalogue began in 2016, when the Department of Health Economics of the Corvinus University of Budapest received support for the organization of an international conference, thus actually starting the process of designing the Hungarian cost library.

During the creation of the Hungarian cost library in Hungary, the Austrian example was considered. Our decision was motivated by the fact that the Austrian 'cost-library' followed a pragmatic methodology, in which a university department of a very similar size to our own, with its similar human resources could achieve a very significant result in a few years. It was also an important aspect that during the joint work with the Austrian department we had the opportunity for continuous consultation, which helped our work greatly.

# 3. HIPOTHESES

## 3.1. Health-related quality of life

*A Comparison of European Polish, Slovenian and British EQ-5D-3L value sets using a Hungarian sample of 18 chronic diseases*

Hypothesis 1.

We assume that the European, Polish, Slovenian and UK EQ-5D-3L value sets do not differ significantly

1.1. We assume that applying different value sets in the 18 chronic diseases that we examined, the health policy and funding decisions based on the results do not differ significantly in different countries.

*A detailed analysis of 'not relevant' responses on the DLQI in psoriasis: potential biases in treatment decisions*

Hypothesis 2.

We assume that the 'not relevant' answers of the DLQI questionnaire differ in the different demographic groups.

2.1. We assume that the effect of the differences on medical decision-making and resource allocation can be observed.

*The health state and productivity of the Hungarian general population*

Hypothesis 3.

We assume that the health status and work productivity of the Hungarian general population can be adequately measured by the standard questionnaires we used.

*Characteristics and determinants of informal care in chronic diseases in Hungary: A comparative analysis*

Hypothesis 4.

We assume that the characteristics and determinants of informal care in Hungary are similar to what can be observed in other countries.

### 3.2. Costing

*Cost of informal care in chronic diseases in Hungary: A comparative analysis*

Hypothesis 5.

We assume that the social burden and cost of informal care is very significant in Hungary as well, in accordance with international experience.

*Cost-of-illness studies in nine Central and Eastern European countries*

Hypothesis 6.

We assume that the costs of illness in Hungary are similar to those in other Central and Eastern European countries.

6.1. We assume that in Hungary the cost data published in other Central Eastern European country can be utilized and transferred better than the cost data originated in countries with high national income.

*Hungarian cost library*

*Hypothesis 7.*

We assume that a Hungarian cost library can be created as sufficient local data is available.

7.1. We assume that the Hungarian cost library can contribute to the development of appropriate and sustainable health care financing decisions.

7.2. We assume that the Hungarian unit costs and cost are significantly different than what can be observed in high-income countries

## 4. OBJECTIVES

### 4.1. Health-related quality of life

### 4.1.1. A Comparison of European Polish, Slovenian and British EQ-5D-3L value sets using a Hungarian sample of 18 chronic diseases

We aimed to compare the Slovenian, Polish, British and European EQ-5D-3L value sets, which are most commonly used or are potentially applicable for health economic evaluations in the CEE region. Our study was based on the comparative analysis of patient level data from cross-sectional surveys conducted in Hungary among patient populations in 18 different chronic conditions. We explored the differences of the EQ-5D-3L index scores calculated with the four value sets by diagnosis, age group and disease severity. Furthermore, we analysed the potential impact of the choice of value sets on health priority setting by comparing the disease burden evaluations across different conditions using different value sets.

### 4.1.2. A detailed analysis of 'not relevant' responses on the DLQI in psoriasis: potential biases in treatment decisions

Our objective was to explore the occurrence of NRRs on the DLQI on a large sample of psoriasis patients and to examine the effect of several socio-demographic and clinical factors on giving NRRs.

### 4.1.3. The health state and productivity of the Hungarian general population

We aimed to assess the health state, well-being and productivity loss experienced by the Hungarian general population with questionnaires like the ICECAP, WPAI and EQ-5D-5L, which are suitable for evaluating outcomes and contributing to

the evaluation of strategy-making in a number of sectors (health-social sector, labour market).

### 4.1.4. Characteristics and determinants of informal care in chronic diseases in Hungary: A comparative analysis

The aim of our research was to analyse the characteristics and determinants of informal car in chronic conditions, with a special attention to observing the relationship between patients' health-related quality of life (measured by the EQ-5D questionnaire) and informal care. We performed a comparative analysis of previous studies.

### 4.2. Costing

### 4.2.1. Cost of informal care in chronic diseases in Hungary: A comparative analysis

Our aim was to analyse the cost of informal care in chronic disease. We performed a comparative analysis in 13 different chronic diseases. We analysis previous studies where patient level data was available.

### 4.2.2. Cost-of-illness studies in nine Central and Eastern European countries

This review has been undertaken to provide a description of the COI studies in nine CEE countries, namely Austria, Bulgaria, the Czech Republic, Croatia, Hungary, Poland, Romania, Slovakia, Slovenia, in the past ten years. The main objectives were to describe study characteristics, methodology and the COI estimates reported.

### 4.2.3. Hungarian cost library

Our aim was to create a Hungarian cost library, containing country specific cost data. We aimed to analyse the possibilities of using the database for providing information in health policy decision making and financing in Hungary.

## 5. METHODS

### 5.1. Health-related quality of life

### 5.1.1. A Comparison of European Polish, Slovenian and British EQ-5D-3L value sets using a Hungarian sample of 18 chronic diseases

5.1.1.1. EQ-5D-3L value sets

The EQ-5D-3L value set has been developed in several countries. However, in the Central and Eastern European region, only Poland and Slovenia have their own set of country-specific values. In the countries of the region, the United Kingdom (hereafter UK) utility value set was often used for evaluation (Devlin et al., 2017), for example, in Hungary it was also used in population surveys (Baji et al., 2015, EuroQolGroup, Dolan, 1997, Rencz et al., 2016). The European value set was developed for international use, with the involvement of 6 countries, however, its application is currently not widespread in the countries of the region (Greiner et al., 2003, Rencz et al., 2016). In the present study, we compared four value sets: the value sets of Poland, Slovenia, the EU, and the United Kingdom (UK).

5.1.1.2. Sample

This current study is a secondary analysis of 18 previous surveys conducted by the Department of Health Economics of the Corvinus University of Budapest. We only included those patients in our analysis, who had answers in all five EQ-5D-3L dimensions; hence EQ-5D-3L index scores could be calculated using the four different value sets.

## 5.1.1.3. Statistical analysis

We applied descriptive methods and graphical representation of key findings. As sample sizes varied substantially across the datasets (min: N=61, max: N=249), analytical weights were constructed to make the pooled dataset a balanced sample of the 18 diseases. The sum of weights was set to 100 by each condition. We calculated weighted mean and percentage values when reporting characteristics of the pooled sample totals. We compared the four value sets by 1) EQ-5D-3L dimensions, 2) by diagnosis, 3) by respondents' subjective health assessment (EQ VAS) and 4) by age group, according to the following. 1) When comparing value sets by EQ-5D-3L dimensions, we graphically represented indices of health states with moderate and severe levels of isolated problems in each dimension (e.g. 21111, 31111 etc.), as well as the combinations of moderate and severe problems (21122, 22222, 32233, 33333) against full health (11111). This comparison allows us to take into account the full disutility arising from the severity of problems and the dimension-specific preferences. Although the distribution of index values was not normal, the sample size was sufficiently large to allow the comparison of diagnosis subgroups using two-sided paired t-tests. Finally, for each value set, we calculated a so-called disease burden (DB) value and its sensitivity to the choice of value set.

## 5.1.2. A detailed analysis of 'not relevant' responses on the DLQI in psoriasis: potential biases in treatment decisions

## 5.1.2.1. Questionnaire survey

We performed two cross-sectional questionnaire surveys in Hungary, in two clinics, among patients suffering from psoriasis. The first study was conducted between 2012 and 2013, involving 200 patients, and the second questionnaire survey was conducted between 2015 and 2016, involving 238 patients with psoriasis in different disease severity. The responses of patients included in both questionnaire surveys were considered only once, and patients whose DLQI

scores could not be calculated due to missing data were excluded, so a total of 428 patients were included in our sample.

## 5.1.2.2. Outcome measures

To assess the health-related quality of life of the patients, we used the EQ-5D-3L questionnaire. The EQ-5D-3L questionnaire was used to assess the general health of the patients. The DLQI questionnaire was used to measure disease-specific quality of life. To assess the severity of the disease, the so-called The "Psoriasis Area Severity Index" (PASI) score was used, which can range from 0 to 72, is used, with higher values indicating higher disease severity.

## 5.1.2.3. Statistical analysis

Descriptive statistics were performed for our whole sample. Subgroups were formed based on DLQI scores. Two methods were used to evaluate 'not relevant' DLQI responses: the frequency of 'not relevant' DLQI responses was determined, and the number of 'not relevant' DLQI responses per patient (which ranged from 0 to 8) was determined.

Due to the non-normal distribution of our data, we used non-parametric tests. To explore the determinants of irrelevant responses, we constructed a multivariate logistic regression model. The relationship between gender and irrelevant responses was examined using a chi-square test. The analyses were performed using IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp. (2013).

### 5.1.3. The health state and productivity of the Hungarian general population

5.1.3.1.    Questionnaire survey

We conducted a cross - sectional questionnaire survey in May - June 2019 on a sample representative of the most important demographic characteristics of the Hungarian population. Ethical approval for the questionnaire was granted by the Scientific and Research Ethics Committee (approval number: 10058-3 / 2019 / EKU). Participants gave their consent to participate in the study.

The questionnaire survey was part of a larger population-based survey (Baji et al., 2019, Péntek et al., 2020). In order to assess the health status and working capacity of the Hungarian population, we focused on the following sections:

•Socio-demographic characteristics: age, gender, education, marital status

•Employment situation

•Characteristics of the respondent's household (household size, net monthly income, type and place of residence)

•Health status of the respondent

•Productivity of the respondent

5.1.3.2.    Outcome measures

To measure labour productivity loss, the WPAI-GH questionnaire presented earlier in the dissertation, the EQ-5D questionnaire to assess the health status of participants, the MEHM (Minimum European Health Module) and ICECAP-A (respondents under 65) and ICECAP-O (Respondents older than 65 years) were used. The UK tariff was used to evaluate the ICECAP questionnaire.

### 5.1.3.3. Statistical analysis

A database was constructed from the data from the questionnaires in IBM SPSS Statistics 25 (IBM SPSS, Version 25.0. Armonk, NY: IBM Corp., 2012). Descriptive statistics were performed to characterize participants 'labour productivity, health status, and well-being. To measure the loss of labour productivity measured by the WPAI questionnaire, a subgroup analysis was performed. Non-parametric tests (Kruskal-Wallis and Mann-Whitney U tests) were used to test the significance of the differences. To explore correlations between different measures, we calculated pairwise Spearman rank correlations due to the non-normal distribution of our variables.

## 5.1.4. Characteristics and determinants of informal care in chronic diseases in Hungary: A comparative analysis

### 5.1.4.1. Surveys included in our analysis

We reviewed the questionnaire research conducted by the Department of Health Economics of the Corvinus University of Budapest in recent years. The studies were selected where informal care in chronic diseases among Hungarian patients was measured in the framework of a cross-sectional survey, the so-called EQ-5D questionnaires' 3L version (see above) was also completed and (anonymized) patient-level data were available.

### 5.1.4.2. Measuring informal care

To assess the informal care use, a series of questions compiled by the Department were used in the studies, except in the case of dementia, which is therefore discussed separately. Informal care was assessed uniformly for the past week, and in each case, the patients themselves answered the questions. In most studies, patients had to report the number of hours they had taken in the past week, with

the exception of epilepsy, benign prostatic hyperplasia (BPH) and osteoporosis, where the number of occasion and the number of hours/occasion were assessed. For bladder cancer (BC), the answers to the questions on weekly informal care and the number of hours per occasion were incomplete, so this variable was not included in the analyses of informal care hours.

The dementia survey was conducted as part of an international study and used to measure the use of formal and informal resources using a special standard questionnaire developed specifically for the dementia survey, which also included questions on informal care (Érsek et al., 2010). The Resource Utilization in Dementia (RUD) is a standard questionnaire that is suitable for comparing resource use and costs for dementia in different countries. The questionnaire was widely used, the Hungarian version of RUD was used in the research (EuroQolGroup, 1990). In our analysis, we compared the one-month informal care periods from the RUD questionnaire to the number of hours per week.

The time of assistance received from another person was normally maximized at 24 hours per day (i.e., 168 hours per week) per patient. While we ruled out cases where the patient admitted to being treated for more than 24 hours, which is actually possible if more caregivers help and supervise the patient, we wanted to avoid overestimating informal care. Secondary analysis was performed using a more conservative approach, maximizing the number of hours of informal care per patient at 8 per day (i.e., 56 hours per week).

5.1.4.3.    Health state measure by the EQ-5D questionnaire

The validated Hungarian version of EQ-5D-3L was used in the selected studies, the UK utility value set was used for the evaluation. (Devlin et al., 2017).

5.1.4.4.    Database

Patient-level data were collected from the original databases in a standard manner and recorded in IBM SPSS Statistics (IBM SPSS, Version 21.0. Armonk, NY:

IBM Corp., 2012). We recorded the type of disease, the age of the patients, the sex of the patients, their educational attainment, their housing situation, the time since the diagnosis, the five dimensions of EQ-5D-3L and the health status of EQ as measured by VAS, and the informal care weekly hours.

### 5.1.4.5.    Statistical analysis

We performed descriptive statistics to describe the demographic attribute, informal care use and health-related quality of life of the patients. We performed sub-group analysis by diagnosis and informal care use. Due to the non-normal distribution of our data, we used non-parametric tests. To analyse the relationship between the EQ-5D, EQ VAS and the informal care time, we used Spearman's rank correlations. To explore the determinants of informal care time, we built a linear regression model.

## 5.2.    Costing

### 5.2.1.  Cost of informal care in chronic diseases in Hungary: A comparative analysis

#### 5.2.1.1.    Sample

The detailed methodology has been published previously (Beretzky et al., 2017). We reviewed those questionnaire surveys conducted by the Department of Health Economics of the Corvinus University of Budapest in recent years, that covered the survey of informal care and used the previously presented EQ-5D-3L questionnaire suitable for measuring health status. The research used a series of questionnaires compiled by the department and completed by patients to measure informal care for the week prior to completion. A secondary analysis of the results of a total of 13 studies was performed in the following disease areas: psoriatic arthritis (AP) (Brodszky et al., 2009), age-related macular degeneration (AMD) (Brodszky et al., 2014a), dementia (Érsek et al., 2010), endometriosis (Simoens

et al., 2012), epilepsy (Pentek et al., 2013), benign prostatic hyperplasia (BPH) (Rencz et al., 2015c), osteoporosis (Péntek et al., 2016b), Parkinson's disease (Tamás et al., 2014), psoriasis (Balogh et al., 2014, Rencz et al., 2014), rheumatoid arthritis (RA) (Péntek et al., 2007), systemic sclerosis (SSc) (Minier et al., 2010), multiple sclerosis (SM) (Péntek et al., 2012b) and schizophrenia (Péntek et al., 2012c).

### 5.2.1.2.    Health-related quality of life

To measure the health-related quality of life, we used the Hungarian version of the EQ-5D-3L questionnaire. We wanted to pay special attention to patients in the worst health states. In order to do this, we selected those who has and EQ-5D-3L index score 0 or lower.

### 5.2.1.3.    Informal care

To avoid overestimating the informal care use, we maximized the informal care hours in 24 hours daily (168 hours weekly). In our secondary analysis, we used a more conservative approach, where we maximized the informal care hours in 8 hours/day. To calculate the cost of informal care we multiplied the number of hours of informal care with the average net hourly wage, which was 973 HUF in 2017 (KSH, 2017).

## 5.2.2.    Cost-of-illness studies in nine Central and Eastern European countries

### 5.2.2.1. Selection of the publications

We conducted a literature search in the Medline, EMBASE, The Cochrane Library, CINAHL, and Web of Science databases to identify publications containing the cost of illness data. The search strategy consisted of a combination of the search term "cost of illness" and the term "Hungary".

Our search reviewed publications in English and Hungarian published between January 1, 2006 and June 30, 2017.

After the search, we examined the results by title and abstract, and then in the second round, we examined the full text and decided on their selection. Reports published exclusively in the abstract and review were excluded.

Publications were selected based on the following criteria: 1. contained cost of illness data for a specific disease, 2. the publication was an original publication, 3. the publication was fully available, 4. the patient population in the publication originated from Austria, Bulgaria, the Czech Republic, Croatia, Hungary Slovenia, Slovakia, Romania or Poland.

5.2.2.2.Database

We summarized the most important data of the selected publications (year of publication, place, language and financial support status) in a summary table, created in Microsoft Excel. In addition, the perspective used in the publication, the name of the diagnosis / intervention in the publication and the cost data included in the selected publications were also identified and recorded

### 5.2.3. Hungarian cost library

The literature search was conducted in four steps, with the search for cost of illness publications, cost-effectiveness, budget-impact analysis publications, and in the case of Hungarian, Hungarian language literature, we performed a manual search. When we refreshed our search, we performed a free word search for the term "cost".

The search was conducted as follows:

1. search for cost of illness publications, time period: January 1, 2006 - June 30, 2017

2. cost-effectiveness, budget-impact analysis search for publications, time period: 1 January 2006 - 30 June 2017

3. manual search in Hungarian literature in Hungarian, time period: January 1, 2006 - March 21, 2020

4. update of our search to identify the latest publications. period: 1 July 2017 - 21 March 2020

5.2.3.1. Cost of illness studies

We conducted a literature search in the Medline, EMBASE, The Cochrane Library, CINAHL, and Web of Science databases to identify publications containing the cost of a disease. The search strategy consisted of a combination of the search term "cost of illness" and the term "Hungary".

Our search reviewed publications in English and Hungarian published between January 1, 2006 and June 30, 2017.

After the search, we examined the results by title and abstract, and then in the second round, we examined their full text and decided on their selection. Reports published exclusively in the abstract and review were excluded.

We applied the following criteria, to identify the publications:

1. included cost of illness data for a specific disease,
2. were original communications, were fully available,
3. the patient population included in the study was selected in Hungary.

5.2.3.2. Cost-effectiveness, budget-impact analysis

In order to identify cost-effectiveness, budget-impact analysis analyses, we searched the OVID MEDLINE database. Our search reviewed publications in English and Hungarian published between January 1, 2006 and June 30, 2017. After the search, we examined the results by title and abstract, and then in the second round, we examined their full text and decided on their selection. Reports published exclusively in the abstract and review were excluded.

From the results, the following publications were selected:

1. included cost-effectiveness, budget impact analysis or cost of illness analysis, or any unit cost data

2. were original, fully available publication,

3. the patient population included in the study was selected in Hungary.

5.2.3.3. Manual search in the Hungarian literature

In order to identify non-indexed, local literature, we conducted a manual search of the searchable database of the contents of Hungarian-language journals (MATARKA, https://matarka.hu/), which lists the contents of scientific and professional journals published in Hungary in a searchable form. After reviewing the relevant results, the original announcements containing data on some disease cost and cost-effectiveness were selected.

Our literature review also included a review of relevant technology analysis reports. Technology analysis reports prepared by the Department of Health Economics (and its predecessors) of the Corvinus University of Budapest, which have an ISBN number, are publicly available and provide domestic cost data for a specific disease / therapy, have been selected. No technology analysis report discussing any specific diagnosis or intervention is available on the website of the National Health Insurance Fund and its successors (National Health Insurance Fund Manager) (http://www.neak.gov.hu/felso_menu/szakmai_oldalak). The archive of the formerly operating Strategic Health Research Institute (ESKI) is no longer available on the website of the Ministry of National Resources (https://www.kormany.hu/hu/emberi-eroforrasokminiszteriuma/egeszsegugyert-felelos-allamtitkarsag). The currently available publications of the current State Center for Health Care (ÁEEK; before March 1, 2015: Institute of Pharmaceutical and Health Quality and Organizational Development) (ERA-Health Systems Database) did not include a technology analysis report on a specific diagnosis or cost-effectiveness of an intervention (AEEK, 2019b, AEEK, 2019a).

### 5.2.3.4.Update of the search

To identify publications published between July 1, 2017, and March 21, 2020, we conducted a free-text search using the "cost" search term in the PubMed Medline database. The term "Hungary" was also marked in the search and the search period to be searched was marked. The results were reviewed and sorted as follows: In this case, the articles published only in the abstract form and the review articles were excluded. After that, the results were examined by title and abstract, and in the second round, after examining their full text, we decided on their selection, according to the following criteria:

1. included cost data for a disease or intervention, or non-disease-specific health costs

2. original communications and were fully available,

3. the patient population included in the publication was selected in Hungary.

When updating the search, in order not to lose results, we continued the "cost" free-text search strategy, which resulted in a number of irrelevant or non-health economics publications appearing in our results, which were excluded.

### 5.2.3.5.     Hungarian cost library

The most important data of the selected publications (year of publication, year of cost calculation, perspective used in the publication, name of the diagnosis / intervention in the publication) and the cost data in them were summarized in a summary table in Microsoft Excel.

Costs were categorized by textbook breakdown (Gulácsi et al., 2012): direct health costs, direct non-health costs, and indirect costs. Within the main cost categories, costs were classified according to whether we could separate costs incurred in outpatient or inpatient care.

The Hungarian cost library also includes the costs of products and services not financed by social security, which have been treated separately. In the case of the

costs included in the publications, we wanted to identify in each case what sources the authors used to calculate the given cost. If disclosed in a particular publication, the unit costs used to calculate the costs have also been considered and recognized. The cost data identified in the publications were also classified according to the form and time period in which the costs were reported.

# 6. RESULTS

## 6.1. Health-related quality of life

### 6.1.1. A Comparison of European Polish, Slovenian and British EQ-5D-3L value sets using a Hungarian sample of 18 chronic diseases

6.1.1.1. Sample

The 18 chronic diseases belonged to 9 different ICD-10 groups. Our total sample included 2421 patients with psoriatic arthritis (PsA) (Brodszky et al., 2009), age-related macular degeneration (AMD) (Brodszky et al., 2010d), attention deficit hyperactivity disorder (ADHD) (Pulay et al., 2016), dementia (Érsek et al., 2010), diabetes (DM) (Brodszky et al., 2010d), endometriosis (ENDO) (Simoens et al., 2012), epilepsy (Pentek et al., 2013), bladder cancer (BC) (Hever et al., 2015), benign prostatic hyperplasia (BPH) (Rencz et al., 2015a), osteoporosis (OP) (Rencz et al., 2016), peripheral arterial occlusive disease (PAOD) (Balogh et al., 2013), Parkinson's disease (PD) (Tamás et al., 2014), psoriasis (PSO) (Rencz et al., 2014, Balogh et al., 2014), rheumatoid arthritis (RA) (Péntek et al., 2007), overactive bladder (OAB) (Péntek et al., 2012a), systemic sclerosis (SSc) (Minier et al., 2010), multiple sclerosis (MS) (Péntek et al., 2012b) and schizophrenia (SCZ) (Péntek et al., 2012c). (Table 1.)

The mean age of the patients was 55.87 (SD = 17.75) years. More than half of the patients were older than 70 years with dementia, age-related macular degeneration, benign prostatic hyperplasia, and peripheral arterial vascular disease. More than half of the patients were women (n = 1356, 58.6%) and it is important to mention that in some diseases only female patients were included in our sample (endometriosis, osteoporosis, hyperactive bladder syndrome) even in benign prostatic hyperplasia only men. The mean disease duration in our sample was 8.75 (SD = 8.95) years, with a distinctly high mean disease duration for psoriasis and epilepsy. (Table 1.)

**Table 1. Demographic characteristics of the sample**

| Diagnosis | Number of patients (n) | Disease duration (year) | Age mean (SD) | Female n (%) |
|---|---|---|---|---|
| Psoriatic arthritis | 177 | 9.30 (9.24) | 49.89 (12.76) | 101 (57.1%) |
| Psoriasis | 192 | 21.66 (11.77) | 50.49 (12.79) | 61 (31.8%) |
| Peripheral arterial occlusive disease | 103 | NA | 70.00 (10.21) | 45 (43.7%) |
| Age-related macular degeneration | 122 | 2.94 (2.54) | 75.16 (7.88) | 76 (62.3%) |
| Rheumatoid arthritis | 249 | 9.15 (9.33) | 55.38 (12.32) | 214 (86.3%) |
| Systemic sclerosis | 80 | 7.16 (6.63) | 57.39 (9.60) | 72 (90.0%) |
| Dementia | 86 | NA | 77.61 (8.60) | 51 (60.0%) |
| Diabetes | 264 | NA | 61.31 (10.98) | 151 (57.2%) |
| Endometriosis | 79 | 7.68 (6.33) | 32.67 (4.80) | 79 (100%) |
| Osteoporosis | 207 | 7.49 (5.60) | 69.57 (8.93) | 207 (100%) |
| Attention deficit hyperactivity disorder | 75 | NA | 30.44 (10.49) | 17 (22.7%) |
| Bladder cancer | 148 | 3.56 (3.78) | 66.24 (9.61) | 50 (33.8%) |
| Benign prostatic hyperplasia | 237 | 5.53 (4.79) | 70.38 (8.18) | 0 (0.0%) |
| Epilepsy | 96 | 15.38 (11.55) | 36.16 (12.12) | 56 (58.3%) |
| Overactive bladder | 61 | NA | 57.72 (11.56) | 61 (100.0%) |
| Parkinson's disease | 99 | 8.08 (5.59) | 62.67 (11.32) | 31 (33.0%) |
| Schizophrenia | 78 | NA | 44.24 (13.05) | 36 (46.2%) |
| Multiple sclerosis | 68 | 7.02 (5.90) | 37.96 (9.08) | 48 (70.6%) |
| Total | 2421 | 8.99 (9.28) | 58.33 (16.41) | 1295.0%) |

NA: not available

6.1.1.2. Problems reported in the EQ-5D-3L dimensions

In our sample, 519 patients (20.7%) did not report a problem in any of the EQ-5D-3L dimensions, and another 420 patients (16.1%) reported a problem (at any level) in all five dimensions. 419 patients (17.6%) reported severe problems in at least one dimension, and even 2002 patients (82.4%) did not report severe problems in any dimension.

The distribution of patients according to the reported problem is shown in Figure 2. The most common problem was in patients with dementia (96.5%), rheumatoid arthritis (95.2%), peripheral arterial disease (95.2%) and psoriatic arthritis (94.4%), and most rarely in endometriosis (44.3%). epilepsy (52.1%) and benign prostatic hyperplasia (53.2%).

Considering our entire sample, the least affected dimension was Self-care, in which 20.5% and 2.6% of patients reported a moderate and severe problem. Most problems were reported by patients in the Pain / discomfort and Anxiety / depression dimensions: moderate problems in 51.7% and 46.5%, severe problems in 10.3% and 9.0%, respectively.

Proportion of those with any level of problem in the dimensions Mobility, Self-sufficiency, Usual activities, Pain / discomfort and Anxiety / depression in the highest peripheral arterial disease (89.3%), rheumatoid arthritis (56.2%), rheumatoid arthritis (20.9%), rheumatoid arthritis (8.4%) and schizophrenia (76.9%). (Figure 2)

Patients with dementia reported severe problems in most cases in the dimensions of Mobility (11.3%), Self-care (19.7%), Usual activities (36.1%) and Anxiety / depression (30.2%), even in the peripheral patients with arterial disease reported the most common serious problem in the Pain / discomfort dimension (31.1%). (Figure 2.)

**Figure 2. Problems reported in the five EQ-5D-3L dimensions by diagnosis**
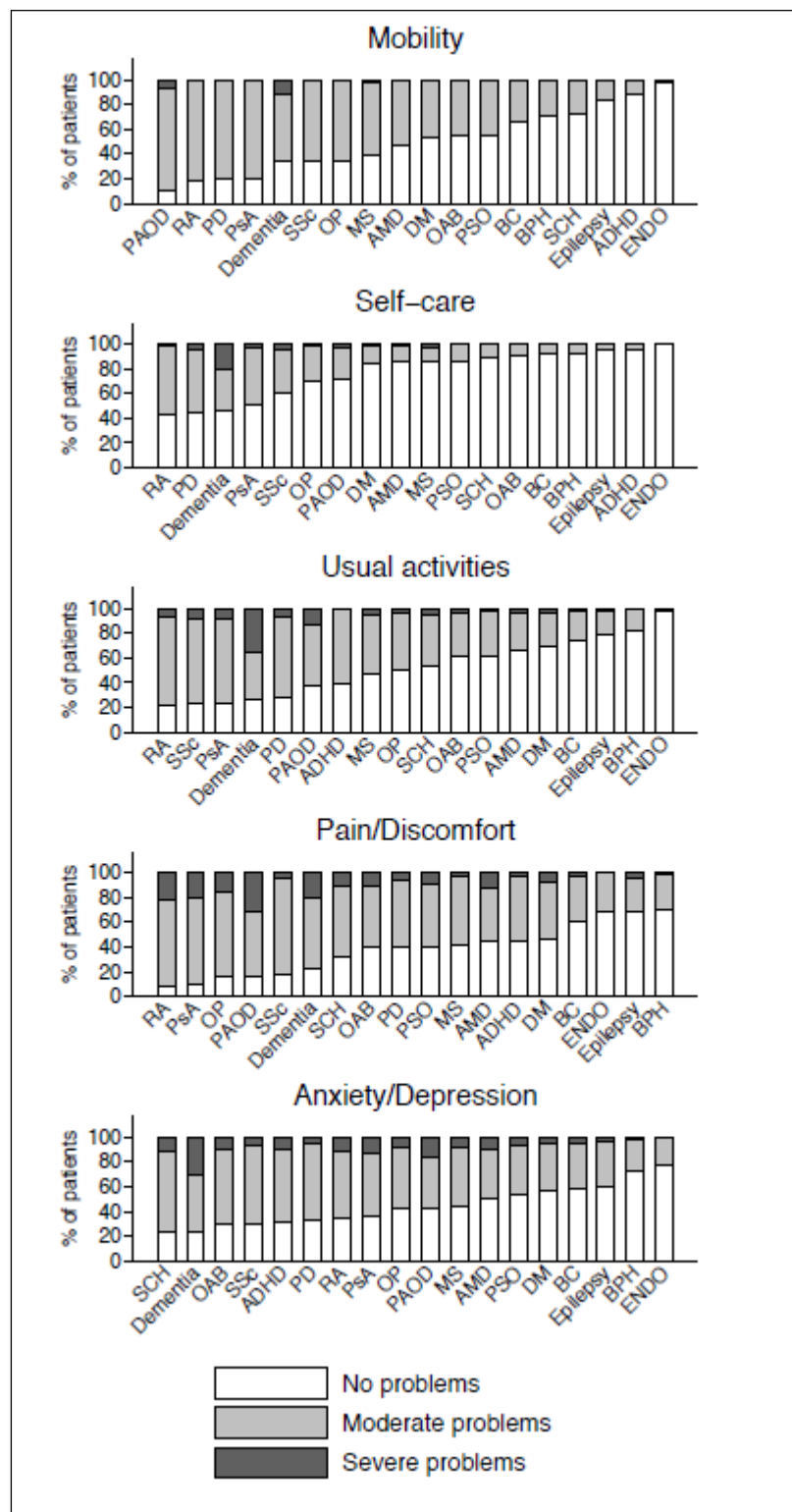


ADHD: attention deficit hyperactivity disorder; AMD: age-related macular degeneration; BC: bladder cancer; BPH: benign prostatic hyperplasia; DM: diabetes mellitus, ENDO: endometriosis; MS: multiple sclerosis; OAB: overactive bladder; OP: osteoporosis; PAOD: peripheral arterial occlusive disease; PsA: psoriatic arthritis; PSO: psoriasis; RA: rheumatoid arthritis; SCZ: schizophrenia; SSc: systemic sclerosis

6.1.1.3. Comparison of EQ-5D-3L value sets


*Comparison of EQ-5D-3L index values by dimensions*

Figure 3 shows the relative significance of the EQ-5D-3L dimensions in the four value sets. With the exception of the severe problem reported in the Usual Activities and Pain / Discomfort dimensions, the Polish value set gave the highest value for moderate or severe problems reported in all dimensions. In the case of moderate problems, in the case of Slovenia, even in the case of severe problems, the UK value set was the lowest.

The loss of utility relative to total health due to the existence of moderate problems was relatively lower for the Polish and UK value sets, but a larger decrease was observed in the presence of severe problems. In the case of the Slovenian value set, the decrease in utility due to moderate problems is accompanied by a larger decrease due to more severe problems. The differences between overall health and moderate problems, as well as measured and severe problems, were similar for the European value set.

In the presence of the most severe problems ('33333'), the UK and Polish value sets provided the lowest values. Of all the possible (243) EQ-5D-3L profiles, the incidence of conditions with a negative utility value ("worse than death") was the most common in the UK value set (35%), followed by Poland (3%), Slovenia (9%) and European (2%) values set followed.

For severe problems, the Polish and UK value sets showed the largest decreases in utility in the Pain / discomfort dimension. In contrast, a serious problem in the Mobility dimension had the greatest negative impact on the EQ-5D-3L index for the use of the Slovenian and European value sets. Based on our results, we expected that both the severity and the location of the reported problem would affect the differences in utility values calculated with the four different value sets. (Figure 3.)

**Figure 3. EQ-5D-3L index scores for selected health states by the four different value sets**
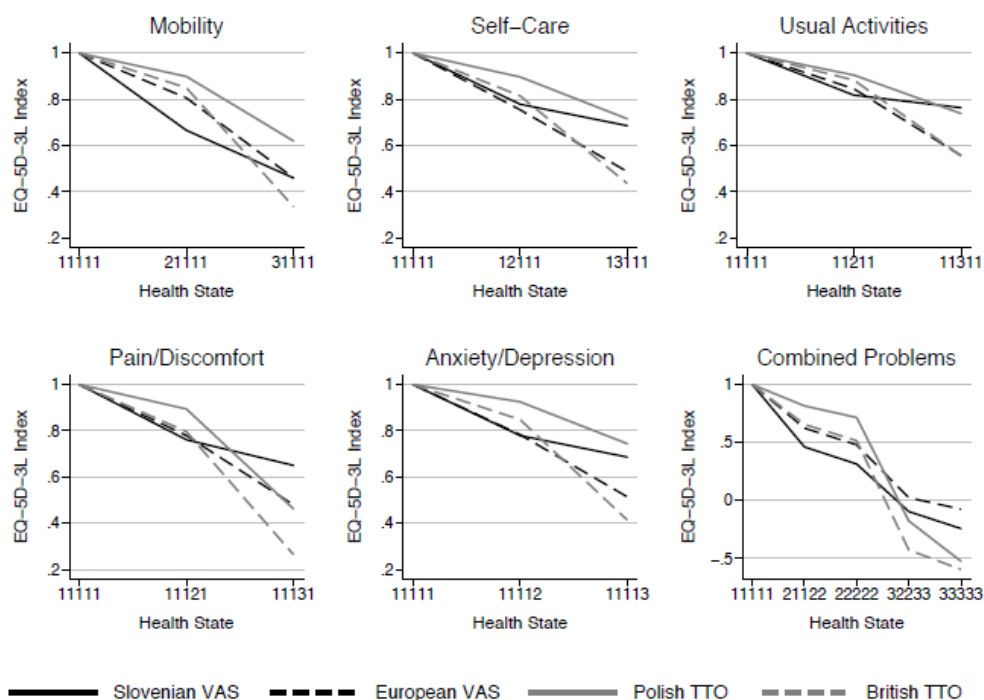


*Comparison of value sets by diagnosis*

For our analysis by diagnosis, we calculated the EQ-5D-3L index values (mean, standard deviation) with all four sets of values in each diagnosis. The weighted average of the EQ-5D-3L index values in our total sample was 0.598 (SD = 0.279), 0.661 (SD = 0.257), 0.770 (SD = 0.261) and 0.644 (SD = 0.334) in Slovenia, Europe, Poland and the UK value sets, respectively. All pairwise value set comparisons showed significant results (p <0.001). (Table 2.)

**Table 2. EQ-5D-3L index scores by diagnosis**

| Diagnosis | EQ-5D-3L index mean (SD) | | | | Two-sided paired t-test p-values | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | SI | EU | UK | PL | SI-EU | SI-PL | SI-UK | PL-UK | PL-EU | UK-EU |
| Rheumatoid arthritis | 0.411 (0.217) | 0.506 (0.235) | 0.464 (0.334) | 0.646 (0.270) | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 |
| Psoriatic arthritis | 0.423 (0.230) | 0.513 (0.244) | 0.467 (0.347) | 0.645 (0.288) | <0.001 | <0.001 | 0.002 | <0.001 | <0.001 | <0.001 |
| Systemic sclerosis | 0.486 (0.240) | 0.583 (0.218) | 0.580 (0.285) | 0.736 (0.234) | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | 0.770 |
| Osteoporosis | 0.519 (0.242) | 0.603 (0.233) | 0.580 (0.319) | 0.729 (0.258) | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | 0.002 |
| Epilepsy | 0.804 (0.229) | 0.826 (0.210) | 0.831 (0.244) | 0.900 (0.166) | 0.001 | <0.001 | 0.006 | <0.001 | <0.001 | 0.384 |
| Multiple sclerosis | 0.586 (0.252) | 0.670 (0.222) | 0.669 (0.278) | 0.795 (0.195) | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | 0.870 |
| Parkinson' disease | 0.476 (0.240) | 0.583 (0.226) | 0.588 (0.281) | 0.741 (0.202) | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | 0.523 |
| Dementia | 0.381 (0.288) | 0.424 (0.286) | 0.333 (0.430) | 0.523 (0.405) | <0.001 | <0.001 | 0.023 | <0.001 | <0.001 | <0.001 |
| Attention deficit hyperactivity disorder | 0.697 (0.188) | 0.727 (0.175) | 0.735 (0.222) | 0.846 (0.142) | <0.001 | <0.001 | 0.005 | <0.001 | <0.001 | 0.320 |
| Schizophrenia | 0.626 (0.214) | 0.658 (0.212) | 0.644 (0.295) | 0.778 (0.227) | 0.002 | <0.001 | 0.320 | <0.001 | <0.001 | 0.261 |
| Endometriosis | 0.880 (0.146) | 0.888 (0.136) | 0.902 (0.124) | 0.950 (0.066) | 0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 |
| Benign prostatic hyperplasia | 0.792 (0.228) | 0.838 (0.181) | 0.852 (0.187) | 0.913 (0.114) | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 |
| Overactive bladder | 0.611 (0.256) | 0.678 (0.227) | 0.668 (0.314) | 0.787 (0.253) | <0.001 | <0.001 | 0.005 | <0.001 | <0.001 | 0.489 |
| Psoriasis | 0.647 (0.271) | 0.706 (0.246) | 0.694 (0.310) | 0.808 (0.226) | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | 0.056 |
| Bladder cancer | 0.729 (0.236) | 0.775 (0.205) | 0.784 (0.242) | 0.874 (0.152) | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | 0.051 |
| Diabetes | 0.665 (0.276) | 0.728 (0.243) | 0.723 (0.295) | 0.826 (0.220) | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | 0.350 |
| Peripheral arterial disease | 0.413 (0.252) | 0.508 (0.274) | 0.426 (0.411) | 0.589 (0.359) | <0.001 | <0.001 | 0.527 | <0.001 | <0.001 | <0.001 |
| Age-related macular degeneration | 0.622 (0.262) | 0.679 (0.250) | 0.657 (0.334) | 0.780 (0.246) | <0.001 | <0.001 | 0.013 | <0.001 | <0.001 | 0.020 |
| Total* | 0.598 (0.279) | 0.661 (0.257) | 0.644 (0.334) | 0.770 (0.261) | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 |

EU: European; PL: Polish; SI: Slovenian; UK:United Kingdom's value set

* Weighted average values

Patients with endometriosis had the highest, and patients suffering from dementia had the lowest mean EQ-5D-3L index value in all four value sets. The largest difference between two value sets was found in the diagnosis of Parkinson's disease between the index values calculated with the Slovenian and Polish value sets (0.265). The comparison of the four value sets with pairwise t-test showed significant differences in most diagnoses. In schizophrenia, the UK value set did not differ significantly from the Slovenian and European value sets. In the other diagnoses, 5 or 6 pairwise comparisons showed significant differences. The UK and European values did not differ significantly in 10 diagnoses, and the UK and Slovenia in 2 of the 18 diagnoses. All other comparisons showed significant differences in all diagnoses.

*Comparison of value sets according to the assessment of patients' subjective health status*

We examined how disease severity affected differences between value sets. Subjective assessment by EQ VAS was used to express disease severity. We were able to identify three well-distinguishable EQ VAS "areas" according to patterns of value set differences. (Figure 4.) The index values calculated with the Polish set of values were the highest in the entire EQ VAS range. The largest difference (between four sets of values) was found in the EQ VAS range between 40 and 80 (n = 437, 61.7%). In this range, the Slovenian index values were the lowest, even the European and UK gave almost the same index score. The smallest differences were found in the range of EQ VAS between 80 and 100 (n = 437, 20.4%), and the value sets showed a difference in the range of EQ VAS below 40 (n = 437, 17.9%), where the Slovenian and Polish stocks converged, while the UK stocks showed the lowest values. (Figure 4.)

**Figure 4. Comparison of value sets by patients' subjective health assessment**
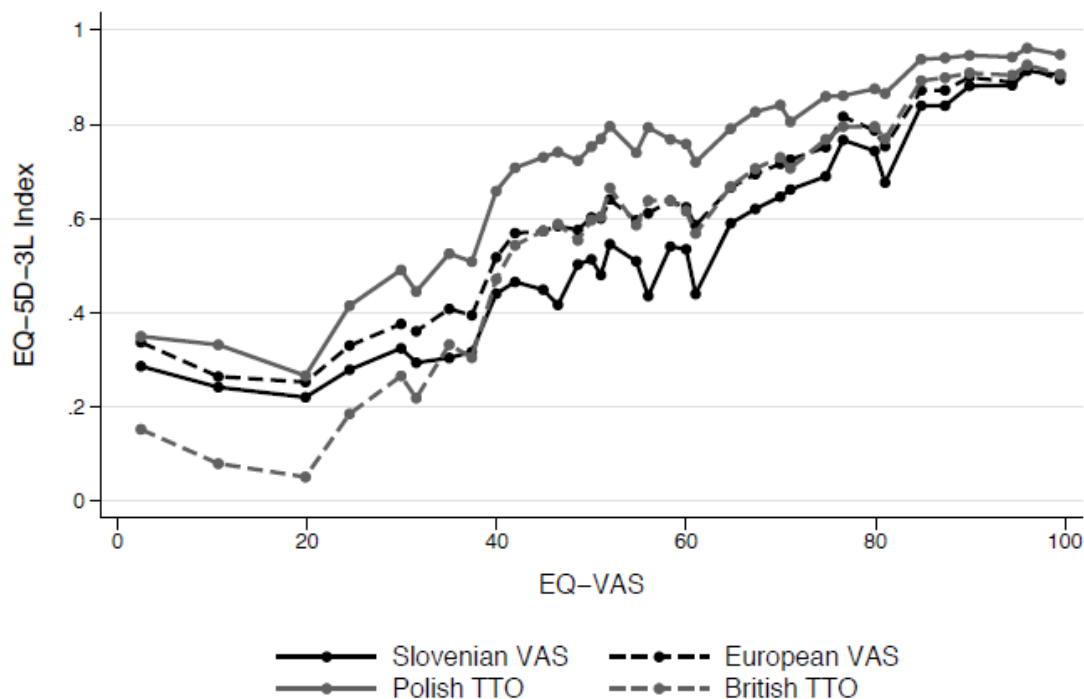


*Comparison of value sets in different age groups*

We also wanted to analyse how the differences in EQ-5D-3L index values calculated with the four different sets of values were influenced by the patient's age. Three age groups were distinguished: those aged 18-34, 35-54, and 55 years. Of the 2421 patients, 16.3% belonged to the youngest (n = 275), 26.7% to the middle (n = 609), and 56.6% (n = 1525) to the oldest age group.

More than half of the patients were in the youngest age group for attention deficit hyperactivity disorder (69.3%), endometriosis (64.6%), and epilepsy (54.2%). In some diseases, which typically affect the elderly population, the majority of patients were over 55 years of age: 100% in elderly macular degeneration, 96.5% in dementia, 95.8% in benign prostatic hyperplasia, 95.2% in peripheral arterial vascular disease, and 93.7% in osteoporosis. The Slovenian, European, Polish and UK index values were 0.765 (SD = 0.214), 0.793 (SD = 0.190), 0.886 (SD = 0.140) and 0.804 (SD = 0.213) in the 18-34 age group, respectively, 0.601 (SD = 0.277), 0.662 (SD = 0.255), 0.773 (SD = 0.251) and 0.644 (SD = 0.329) in the 35-54 age group, and 0.548 (SD = 0.277), 0.622 (SD = 0.262),

0.735 (SD = 0.281) and 0.598 (SD = 0.350) in the group over 55 years of age. All value set comparisons showed significant differences (p≤0.001).

In each age group, the value calculated with the Slovenian value set was the lowest and the Polish value set the highest. The difference between the youngest and oldest age groups was the highest with the Slovenian value set (0.217), followed by the UK (0.206), European (0.171) and Polish (0.150) value sets. Comparison by all age groups showed significant results (p <0.001).

*Sensitivity of disease burden analysis to value set selection*

Despite the fact that the British value set based on the TTO method is most often used both in Hungary and in the Central and Eastern European region (Rencz et al., 2016; Herszényi et al., 2015), we wanted to assess the extent to which disease burden measurement affects the choice of value set in the 18 diagnoses examined. (Figure 5.)

Positive and negative differences were also observed in some diagnoses for all four value sets, with differences in the Slovenian and UK value sets in particular. Values for dementia are 0.15 point lower, even for multiple sclerosis and Parkinson's disease 0.05 points higher, using the Slovenian value set instead of the UK. Polish values differed from British values in the diagnosis of psoriatic arthritis and from European values in dementia. Differences in Polish and Slovenian value sets were also significant in the diagnoses of multiple sclerosis and Parkinson's disease. The value sets yielded very similar index scores in the diagnoses: diabetes, epilepsy, hyperactive bladder syndrome, and osteoporosis.

**Figure 5. Differences of DB evaluations compared to the British TTO value set**
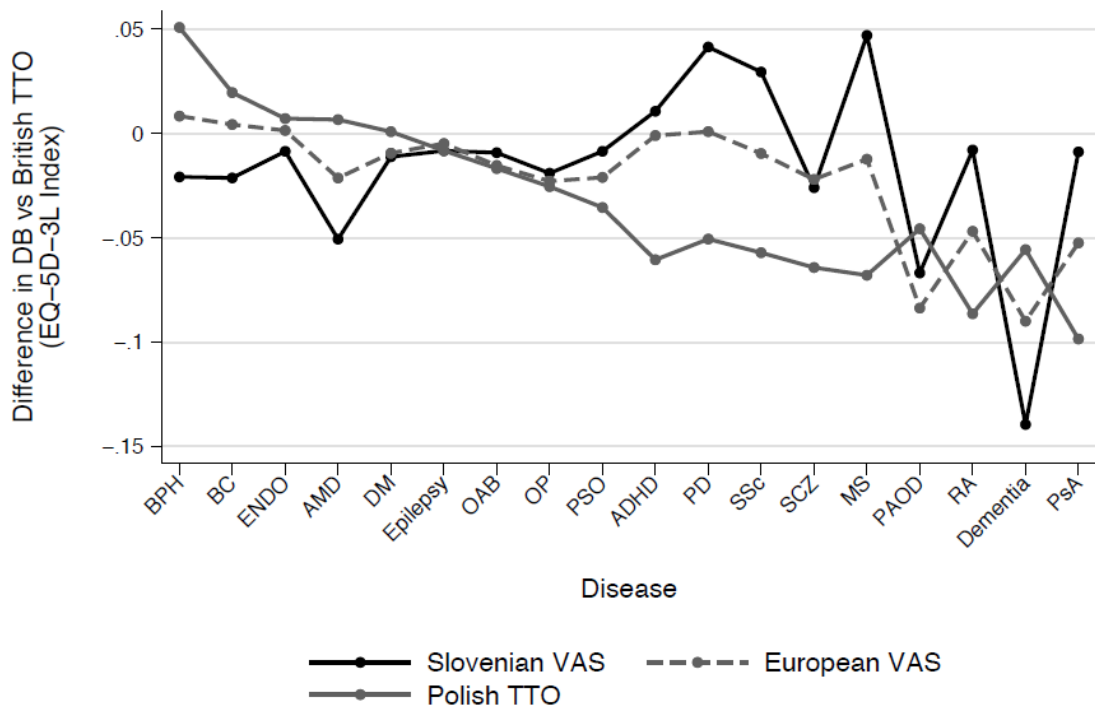


ADHD: attention deficit hyperactivity disorder; AMD: age-related macular degeneration; BC: bladder cancer; BPH: benign prostatic hyperplasia; DM: diabetes mellitus, ENDO: endometriosis; MS: multiple sclerosis; OAB: overactive bladder; OP: osteoporosis; PAOD: peripheral arterial occlusive disease; PsA: psoriatic arthritis; PSO: psoriasis; RA: rheumatoid arthritis; SCZ: schizophrenia; SSc: systemic sclerosis

The "sensitivity index" was used to assess the sensitivity of the value sets. (Table 3) A total of 153 pairwise comparisons were performed in the 18 diagnoses (n = 18 * 17/2), and 22.9% showed mixed results. Combinations of non-significant deviations and significant deviations (in one direction) were the largest deviations. Mainly due to the low number of items in our sample, we did not find a pairwise comparison in which alternative sets of values would have led to a statistically significant, different ranking (+ ΔDB with a given set of values, but - with another). The "sensitivity index" results suggest that different diseases are not equally sensitive to the different value sets. For diagnoses (dementia, multiple sclerosis, and peripheral arterial vascular disease) outcomes were highly dependent on the value set choice, however, in other diagnoses (such as benign prostate enlargement or bladder cancer), results were not significantly affected by the choice of value set.

**Table 3. Sensitivity of disease – disease DB comparisons to the choice of value set (sensitivity index)**

| Diagnosis | Number of comparisons | Pairwise DB differences based on comparing | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | All four value sets[a] | EU vs. PL[c] | EU vs. SI[c] | EU vs. UK[c] | SI vs. PL[c] | SI vs. UK[c] | PL vs. UK[c] |
| Rheumatoid arthritis | 17 | 0.118 | 0.059 | 0.000 | 0.059 | 0.118 | 0.118 | 0.000 |
| Psoriatic arthritis | 17 | 0.176 | 0.118 | 0.000 | 0.118 | 0.118 | 0.118 | 0.000 |
| Systemic sclerosis | 17 | 0.294 | 0.294 | 0.000 | 0.176 | 0.294 | 0.176 | 0.118 |
| Osteoporosis | 17 | 0.235 | 0.235 | 0.000 | 0.118 | 0.235 | 0.118 | 0.118 |
| Epilepsy | 17 | 0.118 | 0.059 | 0.000 | 0.000 | 0.059 | 0.118 | 0.059 |
| Multiple sclerosis | 17 | 0.412 | 0.235 | 0.059 | 0.059 | 0.412 | 0.235 | 0.176 |
| Parkinson's disease | 17 | 0.294 | 0.294 | 0.000 | 0.294 | 0.294 | 0.294 | 0.000 |
| Dementia | 17 | 0.412 | 0.235 | 0.118 | 0.235 | 0.412 | 0.412 | 0.000 |
| Attention deficit hyperactivity disorder | 17 | 0.294 | 0.294 | 0.000 | 0.294 | 0.294 | 0.294 | 0.000 |
| Schizophrenia | 17 | 0.294 | 0.294 | 0.000 | 0.118 | 0.235 | 0.059 | 0.176 |
| Endometriosis | 17 | 0.176 | 0.118 | 0.059 | 0.000 | 0.118 | 0.118 | 0.118 |
| Benign prostatic hyperplasia | 17 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 |
| Overactive bladder | 17 | 0.294 | 0.294 | 0.000 | 0.235 | 0.294 | 0.235 | 0.059 |
| Psoriasis | 17 | 0.294 | 0.235 | 0.118 | 0.235 | 0.235 | 0.235 | 0.000 |
| Bladder cancer | 17 | 0.059 | 0.000 | 0.059 | 0.000 | 0.059 | 0.059 | 0.000 |
| Diabetes | 17 | 0.118 | 0.059 | 0.000 | 0.000 | 0.118 | 0.059 | 0.059 |
| Peripheral arterial occlusive disease | 17 | 0.353 | 0.353 | 0.000 | 0.235 | 0.353 | 0.235 | 0.118 |
| Age-related macular degeneration | 17 | 0.176 | 0.059 | 0.118 | 0.059 | 0.176 | 0.176 | 0.000 |
| Total | 153 | 0.229[b] | 0.180[d] | 0.029[d] | 0.124[d] | 0.212[d] | 0.170[d] | 0.056[d] |

*DB: disease burden, SI: Slovenian; SSc: systemic sclerosis; UK: British, a calculated from 17x4 DB evaluations b calculated from 153x4 DB evaluations. c calculated from 17x2 DB evaluations d calculated from 153x2 DB evaluations

**6.1.2. A detailed analysis of 'not relevant' responses on the DLQI in psoriasis: potential biases in treatment decisions**

6.1.2.1. Characteristics of the patient population

The mean age of patients with psoriasis (n = 428) was 49.2 (SD = 14.3) years and 65% of patients were male. Nearly one-third of the patients had tertiary education and less than one-third had a full-time job. A higher proportion of male patients performed paid work (62.6% vs. 44.7%, p <0.001), however, there was no significant difference between the sexes in terms of education. The mean disease duration was 19.9 and 12.3 years, respectively. More than 80% of patients had moderate-to-severe psoriasis, and the majority of patients (43.7%) received biologic therapy, another 25% received systemic, non-biological, and 24.1% received topical therapy only. A total of 31 patients (7.2%) did not receive any treatment at the time of the study, most had PASI values above 10, and were about to begin systemic therapy.

6.1.2.2. Detailed analysis of the „not relevant" answers

For the items sports (6), sexual difficulties (9), and work or study (7), 28.4%, 16.4%, and 14% chose the NRR answers, respectively. Less than 3% indicated an NRR response for clothing (4), difficulties related to treatment (10), and social events (5). (Figure 6.)

**Figure 6. Distribution of DLQI items according to the number of 'not relevant' responses per patient (%)**
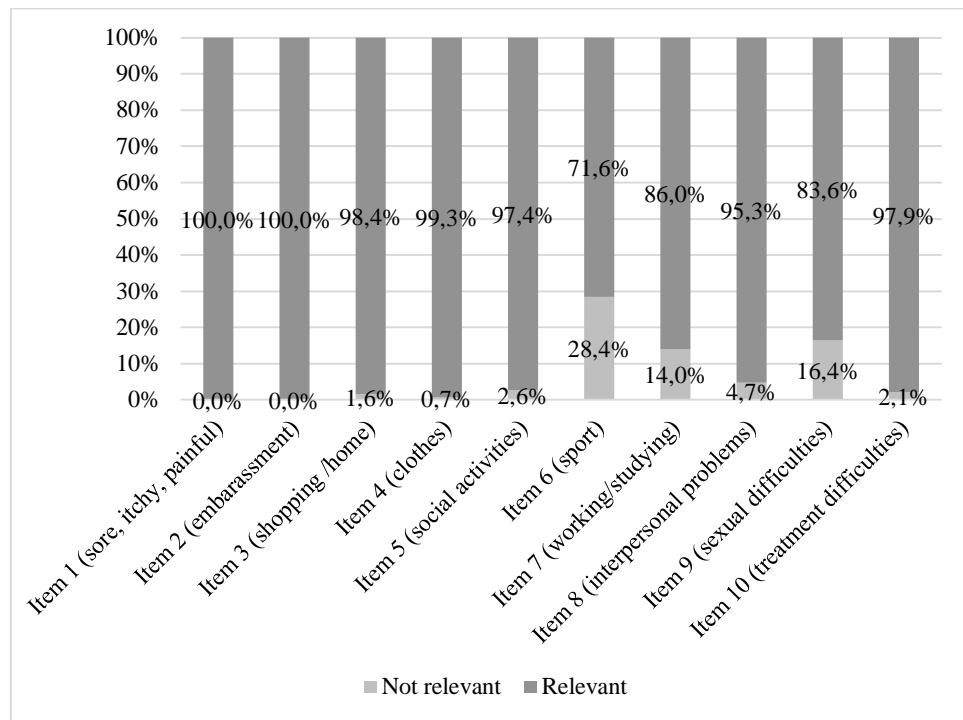


Of the 238 patients, 38.8% (n = 166) reported at least one NRR response. Of these, 84 (19.6%) had one NRR response, 49 (11.5%) had two NRR responses, 22 (5.1%) had 3 NRR responses, 7 patients (1.6%) had 4 NRR responses, 1 had (0.2%) indicated 5 NRR responses, 2 patients (0.5%) reported 6 NRR responses, and one patient (0.2%) reported eight NRR responses. Element 6 (sports) was marked by the majority of those who marked 1 NRR response (61.9%).

Of the patients with a DLQI score of 0 or 1, 28% had at least one NRR response. Of the patients with DLQI scores of 2–5, 6–10, and 11–20, 38%, 52%, and 53% had NRR responses, respectively. For patients with a score above 21, the number of patients with an NRR response was 13%. (Figure 7.)

**Figure 7. Number of 'not relevant' responses by DLQI score bands**
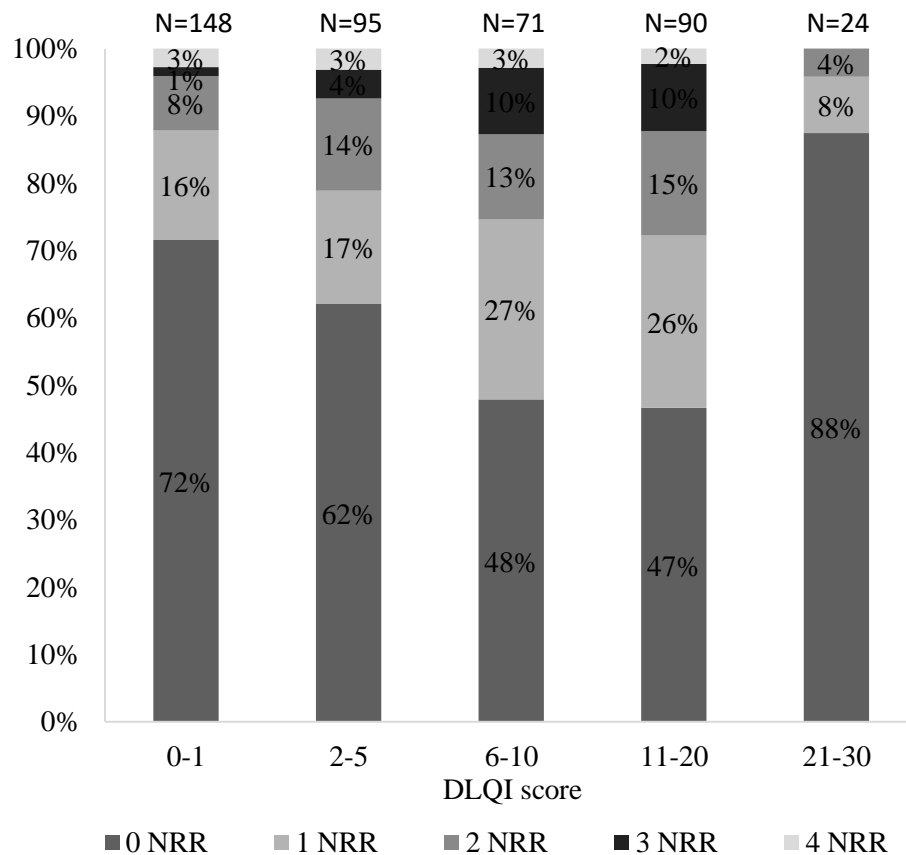


6.1.2.3. Determinant of the 'not relevant' answers

The mean DLQI scores of patients with NRR responses 1, 2, and 3 were 6.5, 7.2, and 7.3, respectively (p = 0.049). In our multivariate logistic regression model, several socio-demographic and clinical factors showed a significant effect on NRR responses. Women were more likely to choose an NRR response. However, the existence of secondary or tertiary education reduced the likelihood of giving NRR responses. Full-time employed respondents were less likely to opt for the NRR response option. Furthermore, higher age and PASI were associated with a higher probability of occurrence of NRR responses. (Table 4.)

**Table 4. Multivariate, logistic regression model**

| Variable | Coefficient | SE | Odds Ratio (95% confidence interval) | p |
|---|---|---|---|---|
| Constant | -1,668 | 0,599 | 0,189 | 0,005 |
| Gender (women) | 0,498 | 0,235 | 1,646 (1,039–2,608) | 0,034 |
| Age (years) | 0,048 | 0,009 | 1,049 (1,031–1,068) | 0,000 |
| PASI score | 0,030 | 0,012 | 1,030 (1,006–1,055) | 0,014 |
| Level of education | | | | |
| Secondary | -0,905 | 0,337 | 0,405 (0,209–0,784) | 0,007 |
| Higher | -0,071 | 0,377 | 0,343 (0,164–0,717) | 0,004 |
| Working full-time | -0,746 | 0,250 | 0,474 (0,290–0,774) | 0,003 |

n=428, dependent variable: 0 NRR response="0", at least 1 NRR response="1"

### 6.1.3. The health state and productivity of the Hungarian general population

6.1.3.1. Characteristics of the sample

A total of 2023 respondents participated in the study, 50.1% of the respondents (n = 1013) were women. The mean age was 48.7 years (SD = 17.9). 41.7% of the respondents had a primary education, 38.1% a secondary education and 20.2% a higher education. 19.7% of the respondents lived in Budapest, 52.5% in other cities and 27.8% in villages. The household of the filling persons had an average of 2.5 (SD = 1.3) members and the average monthly income of the household per capita was 128,000 HUF (SD = 60,000 HUF).

6.1.3.2. Health state

*EQ-5D-5L*

The mean of the EQ-5D-5L index score was 0.92 (SD = 0.15). Most problems were reported by respondents in the Pain / discomfort dimension: 31.6% indicated the existence of some level of problem in this dimension. The mean EQ-VAS was 81.6 (SD = 17.4) among participants. (Table 6.)

Men reported fewer problems than women, with the exception of the Self-care dimension, in which 9.9% and 8.9%, indicated some level of problem respectively. Respondents had mean EQ-5D-5L index and EQ VAS score of 0.92 (SD = 0.15) and 81.6 (SD = 17.4).

MEHM

Altogether 20.6% of respondents rated their current health status as "Very Good" and only 18 respondents (0.9%) stated that their health status was "Very Poor". 31.4% of the respondents (n = 635 people) had a chronic illness or health problem lasting more than 6 months. The majority of respondents (80.4%, n = 1627 people) were not limited by their health problems for more than 6 months, and 3.2% (n = 65 people) indicated that they were severely limited in their daily activities due to health problems. (Table 5)

**Table 5. Respondents current health state (MEHM), N=2023**

| Minimum European Health Module | n (%) |
|---|---|
| **Self-perceived health** | |
| Very good | 417 (20.6%) |
| Good | 916 (45.3%) |
| Fair | 545 (26.9%) |
| Bad | 127 (6.3%) |
| Very bad | 18 (0.9%) |
| **Chronic morbidity** | |
| Yes | 635 (31.4%) |
| No | 1381 (68.8%) |
| Does not want to answer | 7 (0.3%) |
| **Activity limitations** | |
| Severely limited | 65 (3.2%) |
| Limited but not severely | 329 (16.3%) |
| Not limited | 1627 (80.4%) |
| Does not want to answer | 2 (0.1%) |

6.1.3.3. Productivity

Participants worked a median of 40 hours (minimum-maximum: 0-100) hours in the week prior to completing the questionnaire and had a median of 0 hours of absence due to health reasons. The maximum number of hours missed from work was 60 hours (minimum: 0 hours). The median score of absenteeism and presenteeism, and total productivity loss at work, were both 0.

Regarding the questions on employment, 1259 people answered that they work full-time or part-time. Based on the answers to the first question of the WPAI questionnaire, 1232 respondents were in paid employment at the time of the questionnaire survey, the differences may be due to different questions (e.g. if a self-employed respondents indicated that they are not in paid employment). The work-related analyses were based on the responses of 1232 people based on the WPAI questionnaire.

In addition, an additional 4 respondents were excluded from our analysis because the maximum number of hours of possible paid work was 100 hours per week. Another 32 people did not work last week, but not for health reasons. Two participants were excluded due to incomplete responses (the question on disability at work was not completed, but they reported that they worked last week). Our analysis on paid work involved of 1194 respondents. Of these, 25 people did not work, so the decrease in productivity during work was analysed for 1169 people.

The average WPAI productivity loss in other activities was 9.5% (SD = 21.0%), while the average value of total productivity loss at work was 7.7% (SD = 20.9%). For absenteeism and presenteeism, the mean values were 3.6% (16.4%) and 4.4% (14.2%), respectively. We did not find significant differences by gender, we found similar values for women and men in all four variables. According to our analysis by age groups, we found a significant difference between the mean value productivity loss in other activities, the total productivity loss during work and the preseteeism (p = 0.000, in all cases). (Table 6.)

**Table 5. Respondent's socio-economic characteristics and productivity**

| Variable | N (%) | EQ VAS, N=2023 | EQ-5D-3L index, N=2019 | WPAI, other activities, % N=2023 | WPAI, absenteeism, % N=1194 | | WPAI total productivity loss % N=1194 | WPAI presenteeism, %, N=1169 | |
|---|---|---|---|---|---|---|---|---|---|
| | | Mean (SD) | Mean (SD) | Mean (SD) | N (%) | Mean (SD) | Mean (SD) | N (%) | Mean (SD) |
| Total sample | 2023 (100%) | 0.877 (0.204) | 81.6 (17.4) | 9.5 (21.0) | 1194 (100%) | 3.6 (16.4) | 7.7 (20.9) | 1169 (100%) | 4.4 (14.2) |
| **Gender** | | p=0.857 | p=0.012 | p=0.222 | | p=0.448 | p=0.651 | | p=0.879 |
| Men | 1010 (49.9%) | 81.6 (17.4) | 0.886 (0.201) | 8.9 (20.2) | 614 (51.4%) | 4.1 (17.3) | 8.0 (21.2) | 600 (51.3%) | 4.3 (1.3.7) |
| Women | 1013 (50.1%) | 81.6 (17.4) | 0.868 (0.207) | 10.2 (21.8) | 580 (48.5%) | 3.1 (15.4) | 7.3 (20.6) | 569 (48.7%) | 4.7 (15.5) |
| **Age group** | | p=0.000 | p=0.000 | p=0.000 | | p=0.983 | p=0.000 | | p=0.000 |
| 18-24 | 208 (10.3%) | 92.6 (10.3) | 0.923 (0.100) | 1.8 (9.6) | 111 (9.3%) | 4.1 (16.7) | 6.0 (20.4) | 109 (9.3%) | 2.4 (12.9) |
| 25-34 | 308 (15.2%) | 90.7 (11.5) | 0.957 (0.117) | 3.3 (14.0) | 249 (21.7%) | 3.7 (17.2) | 7.5 (22.4) | 243 (20.8%) | 4.3 (16.1) |
| 35-44 | 387 (19.1%) | 86.5 (13.6) | 0.928 (0.174) | 4.2 (13.9) | 329 (27.6%) | 3.2 (15.0) | 6.9 (19.4) | 324 (27.7%) | 4.0 (13.2) |
| 45-54 | 333 (16.5%) | 85.1 (14.1) | 0.925 (0.159) | 5.3 (16.0) | 296 (24.8%) | 3.7 (16.7) | 7.4 (20.6) | 289 (24.7%) | 3.9 (13.0) |
| 55-64 | 334 (16.5%) | 76.6 (17.6) | 0.856 (0.201) | 11.7 (22.5) | 190 (15.9%) | 4.1 (17.6) | 9.7 (22.2) | 185 (15.8%) | 6.0 (14.8) |
| 65-74 | 267 (13.2%) | 70.3 (17.1) | 0.772 (0.216) | 16.8 (24.7) | 19 (1.6%) | 2.6 (11.5) | 14.5 (2.1.8) | 19 (1.6%) | 13.7 (19.2) |
| 75-84 | 145 (7.2%) | 60.3 (16.9) | 0.661 (0.235) | 30.3 (28.9) | - | - | - | - | - |
| 85- | 41 (2.0%) | 57.0 (20.4) | 0.549 (0.332) | 42.9 (32.0) | - | - | - | - | - |
| **Education** | | p=0.000 | p=0.000 | p=0.000 | | p=0.118 | p=0.102 | | p=0.436 |
| Primary | 844 (41.7%) | 75.8 (19.8) | 0.828 (0.235) | 14.8 (25.8) | 400 (33.5%) | 4.8 (19.3) | 9.7 (24.2) | 387 (33.1%) | 5.2 (16.1) |
| Secondary | 770 (38.1%) | 85.6 (14.4) | 0.908 (0.176) | 5.9 (16.4) | 511 (42.8%) | 3.5 (15.8) | 7.5 (20.5) | 502 (42.9%) | 4.5 (14.4) |
| Higher | 409 (20.2%) | 86.1 (13.4) | 0.921 (0.160) | 5.4 (14.5) | 283 (23.7%) | 2.2 (12.5) | 5.0 (15.9) | 280 (24.0%) | 2.9 (10.4) |

| Variable | N (%) | EQ VAS. N=2023 | EQ-5D-3L index. N=2019 | WPAI. other activities. % N=2023 | WPAI. absenteeism. % N=1194 | | WPAI total productivity loss % N=1194 | WPAI presenteeism. %. N=1169 | |
|---|---|---|---|---|---|---|---|---|---|
| | | Mean (SD) | Mean (SD) | Mean (SD) | N (%) | Mean (SD) | Mean (SD) | N (%) | Mean (SD) |
| **Mother's education** | | p=0.000 | p=0.000 | p=0.000 | | p=0.015 | p=0.009 | | p=0.187 |
| Primary | 1283 (63.4%) | 78.0 (18.9) | 0.840 (0.227) | 12.8 (24.0) | 659 (55.2%) | 4.8 (18.9) | 9.6 (23.6) | 640 (54.7%) | 5.2 (15.6) |
| Secondary | 509 (25.2%) | 87.3 (12.5) | 0.938 (0.142) | 3.9 (12.5) | 365 (30.6%) | 2.1 (12.8) | 4.9 (15.9) | 360 (30.8%) | 2.9 (9.9) |
| Higher | 231 (11.4%) | 89.3 (11.3) | 0.949 (0.121) | 4.0 (13.4) | 170 (14.2%) | 2.1 (11.8) | 5.9 (18.6) | 169 (14.5%) | 4.5 (15.9) |
| **Residence** | | p=0.004 | p=0.004 | 0.271 | | p=0.268 | p=0.158 | | p=0.334 |
| Budapest | 399 (19.7%) | 85.5 (14.2) | 0.901 (0.187) | 6.1 (14.3) | 263 (22.0%) | 2.3 (13.4) | 4.8 (15.0) | 259 (22.2%) | 2.6 (7.4) |
| Other city | 1062 (52.5%) | 80.8 (17.8) | 0.871 (0.199) | 10.1 (21.9) | 613 (51.3%) | 3.8 (16.4) | 7.8 (21.0) | 601 (51.4%) | 4.2 (14.0) |
| Other | 562 (27.8%) | 80.4 (18.4) | 0.871 (0.224) | 10.9 (23.2) | 318 (26.7%) | 4.3 (18.5) | 9.7 (24.4) | 309 (26.4%) | 6.0 (18.1) |
| **Marital status** | | p=0.000 | p=0.000 | p=0.000 | | p=0.921 | p=0.004 | | p=0.000 |
| Married | 939 (46.4%) | 81.4 (16.5) | 0.891 (0.179) | 8.0 (18.5) | 576 (48.2%) | 3.2 (14.5) | 6.4 (18.0) | 568 (48.6%) | 3.4 (11.3) |
| In a relationship | 301 (14.9%) | 88.6 (13.1) | 0.940 (0.141) | 3.9 (14.2) | 241 (20.2%) | 5.4 (21.0) | 9.3 (25.1) | 232 (19.8%) | 4.4 (16.3) |
| Single | 387 (19.1%) | 88.3 (14.4) | 0.933 (0.174) | 4.6 (15.9) | 259 (21.7%) | 2.9 (14.5) | 6.6 (19.4) | 255 (21.8%) | 3.9 (13.6) |
| Widow | 207 (10.2%) | 65.4 (18.7) | 0.658 (0.277) | 2.9 (30.5) | 17 (1.4%) | 5.9 (24.3) | 18.8 (30.4) | 16 (1.4%) | 13.8 (22.8) |
| Divorced | 185 (9.1%) | 75.5 (18.1) | 0.835 (0.208) | 15.1 (25.7) | 100 (8.4%) | 3.5 (17.8) | 12.0 (26.0) | 97 (8.3%) | 9.2 (21.0) |
| Other | 4 (0.2%) | 73.8 (23.6) | 0.802 (0.233) | 12.5 (25.0) | 1 (0.1%) | 0.0 | 0.0 | 1 (0.1%) | 0.0 |
| **Married/Living in a relationship** | | p=0.000 | p=0.000 | p=0.000 | | p=0.289 | p=0.263 | | p=0.044 |
| no | 783 (38.7%) | 79.1 (19.2) | 0.837 (0.242) | 13.5 (25.1) | 377 (31.6%) | 3.2 (15.9) | 8.5 (22.1) | 369 (31.6%) | 5.7 (16.5) |
| yes | 1240 (61.3%) | 83.2 (16.0) | 0.903 (0.172) | 7.0 (17.6) | 817 (68.4%) | 3.8 (16.7) | 7.2 (20.4) | 800 (68.4%) | 3.7 (13.0) |

\* Four respondents did not answer all five questions in the descriptive part of the EQ-5D-3L, so their EQ-5D-3L index value could not be calculated for them. \*\* A total of 1232 respondents did paid work, but 32 of them answered that 0 worked hours due to health problems and worked 0 hours last week. In another 27 cases, there was a missing answer to the 'Presenteeism' question. Therefore, data from 1173 respondents were processed for the WPAI labour productivity loss results.

6.1.3.4. Well-being

*ICECAP-A and ICECAP-O*

In the ICECAP-A questionnaire (used for those under 65 years of age (n = 1568)), the highest levels of abilities were found in the dimensions of Attachment, Enjoyment, and Autonomy (59.4%, 56.6%, and 52.6%, respectively). The Outcomes and Progress dimension was not problematic for 43.4% of respondents, and only about half (51.8%) of respondents felt secure in all areas of life.

The ICECAP-O questionnaire was for those aged 65 and over (453 respondents in our sample). Nearly two-thirds (64.9%) of respondents in the Attachment dimension reported some level of problem. In the Enjoyment dimension, this proportion was even higher: 78.4% indicated the existence of any problem. Control (independence) was a problem for the majority (71.1%), and Role (the ability to do valuable things) were generally present (72.8%) as well as Security (thinking about the future without concern) (75, 7%). (Figures 8. and 9.)

Differences by gender were small for both ICECAP questionnaires. The mean of the ICECAP-A index was 0.89 (SD = 0.13), even the mean of the ICECAP-O (over 65 years) index was 0.83 (SD = 0.15).

**Figure 8. ICECAP-A answers by gender (%)**
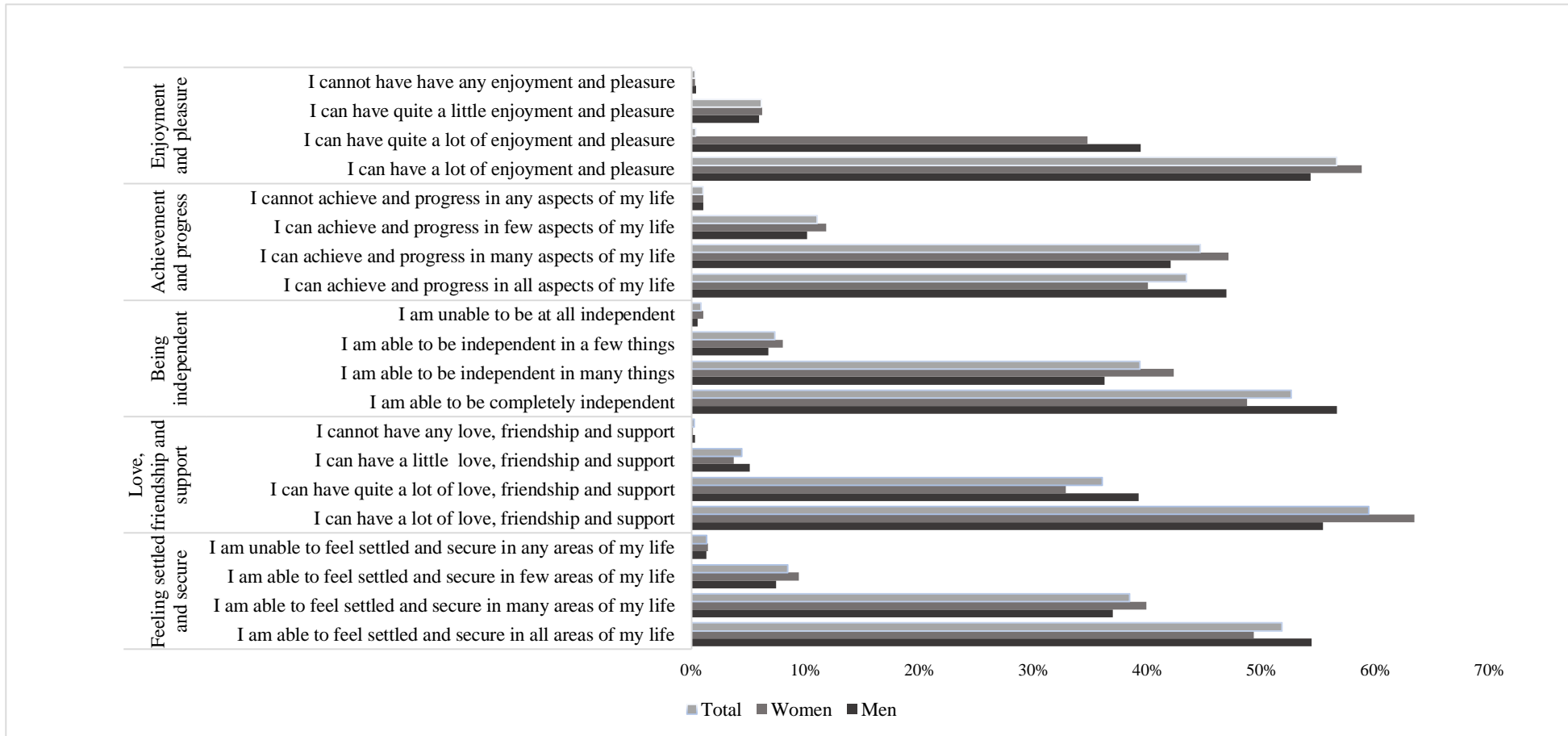
**Figure 9. ICECAP-O answers by gender (%)**
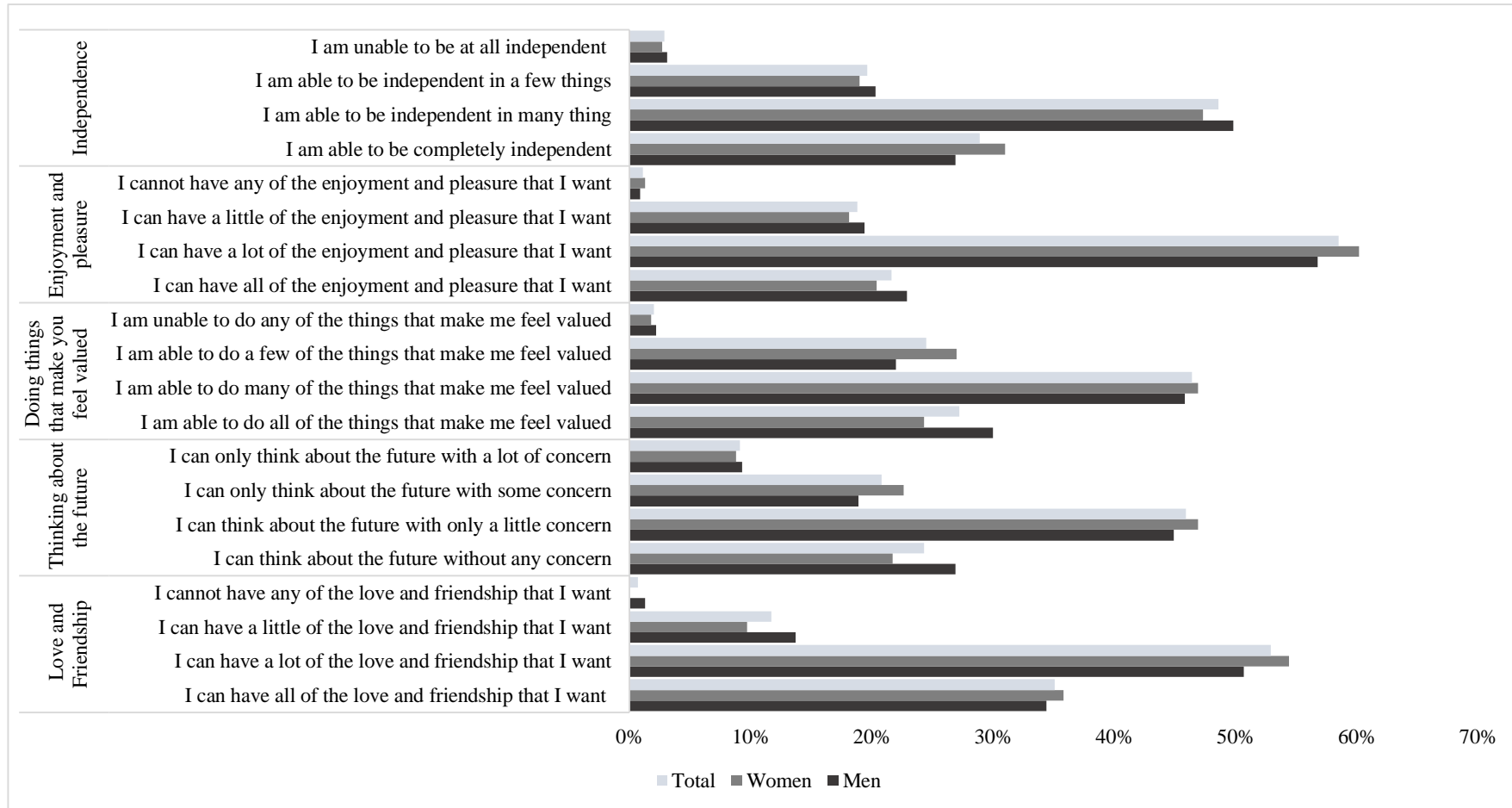
6.1.3.5. Correlations between different measures

To explore the relationship between respondent health, well-being, and productivity, we calculated Spearman's rank correlation. We found a significant negative relationship between the EQ-5D-5L index score and the WPAI absenteeism (r = -0.116), presenteeism (r = -0.399), total productivity loss at work (r = -0.371), and productivity loss in other activities. (r = -0.593) (p <0.001 in all cases). The EQ-5D-3L values showed very similar results: r = -0.116, r = -0.387, r = 0.359, and r = -0.592, respectively (p <0.001 in each case). Out of the WPAI values, the participants' household net monthly income showed a significant relationship only with the productivity loss in other activities (r = -0.277, p = 0.000). ICECAP-A and ICECAP-O values showed a significant negative relationship with WPAI. The age of the respondents showed a positive significant relationship between presenteeism (r = 0.141), total productivity loss at work (r = 0.113) and productivity loss in other activities (r = 0.412) (p <0.001 in all cases). (Table 7.)

**Table 6. Correlations of the different measures**

| | | Abstenteeism (%) | Presenteeism (%) | Total productivity loss at work (%) | Productivity loss in other activities (%) | EQ-5D-5L index score | EQ-5D-3L index score | Age | Net monthly income of the household | ICECAP-A | ICECAP-O |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Abstenteeism (%)** | r | 1 | | | | | | | | | |
| | p | 0.000 | | | | | | | | | |
| **Presenteeism (%)** | r | 0.147** | 1 | | | | | | | | |
| | p | 0.000 | 0.000 | | | | | | | | |
| **Total productivity loss at work (%)** | r | 0.585** | 0.900** | 1 | | | | | | | |
| | p | 0.000 | 0.000 | 0.000 | | | | | | | |
| **Productivity loss in other activities (%)** | r | 0.134** | 0.768** | 0.660** | 1 | | | | | | |
| | p | 0.000 | 0.000 | 0.000 | 0.000 | | | | | | |
| **EQ-5D-5L index score** | r | -0.116** | -0.399** | -0.371** | -0.593** | 1 | | | | | |
| | p | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | | | | | |
| **EQ-5D-3L index score** | r | -0.116** | -0.387** | -0.359** | -0.592** | 0.918** | 1 | | | | |
| | p | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | | | | |
| **Age** | r | 0.008 | 0.141** | 0.113** | 0.412** | -0.500** | -0.490** | 1 | | | |
| | p | 0.782 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | | | |
| **Net monthly income of the household** | r | -0.024 | -0.029 | -0.035 | -0.277** | 0.381** | 0.383** | -0.371** | 1 | | |
| | p | 0.496 | 0.415 | 0.33 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | | |
| **ICECAP-A** | r | -0.070* | -0.212** | -0.196** | -0.281** | 0.469** | 0.462** | -0.210** | 0.221** | 1 | |
| | p | 0.016 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | |
| **ICECAP-O** | r | -0.515* | -0.578** | -0.585** | -0.490** | 0.613** | 0.589** | -0.179** | 0.236** | - | 1 |
| | p | 0.017 | 0.006 | 0.005 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | - | 0.000 |

*significant on a 0.05 level

** significant on a 0.01 level

**6.1.4. Characteristics and determinants of informal care in chronic diseases in Hungary: A comparative analysis**

6.1.4.1. Patients in the sample

A total of 14 different studies met our selection criteria, all of which were performed at different diagnoses. The studies covered a wide range of diseases: psoriatic arthritis (AP) (Brodszky et al., 2009), age-related macular degeneration (AMD) (Péntek et al., 2012a), dementia (Érsek et al., 2010), endometriosis (Simoens et al., 2012), epilepsy (Pentek et al., 2013), bladder cancer (Hever et al., 2015), benign prostatic hyperplasia (BPH) (Rencz et al., 2015c), osteoporosis (Péntek et al., 2016b), Parkinson's disease (Tamás et al., 2014), psoriasis (Rencz et al., 2014, Balogh et al., 2014), rheumatoid arthritis (RA) (Péntek et al., 2007), systemic sclerosis (SSc) (Minier et al., 2010), multiple sclerosis (SM) (Péntek et al., 2012b), schizophrenia (Gulácsi et al., 2012).

A total of 2,047 patients were included in the sample, with a mean age of 58.9 (SD = 16.3) years. 58.0% of the patients were female, with a mean age of 57.8 (SD 16.7) years and a male age of 60.3 (SD = 15.6) years. The three diagnoses with the highest number of patients were osteoporosis (n = 282), RA (n = 255), and benign prostate hyperplasia (n = 246). (Table 8.)

**Table 7. Characteristics of the patients in our sample**

| Diagnosis (reference) | Number of patients (n) | Female (%) | Age, years mean (SD) | Higher education (%) | Living alone (%) | Disease duration, years mean (SD) | EQ-5D-3L index, mean (SD) | EQ VAS, mean (SD) |
|---|---|---|---|---|---|---|---|---|
| Total | 2047 | 58.04% | 58.88 (16.34) | 23.98% | 31.34% | 8.94 (9.17) | 0.64 (0.33) | 60.48 (20.25) |
| Osteoporosis (Péntek et al., 2016b) | 282 | 100.00% | 69.58 (8.58) | 23.32% | 67.38% | 7.28 (5.34) | 0.58 (0.32) | 58.96 (17.06) |
| Rheumatoid arthritis (Péntek et al., 2007) | 255 | 85.83% | 55.45 (12.31) | 16.80% | 22.00% | 9.10 (9.27) | 0.46 (0.33) | 51.65 (19.81) |
| Benign prostatic hyperplasia (Rencz et al., 2015c) | 246 | 0% | 70.59 (8.13) | 25.62% | 12.30% | 5.56 (4.86) | 0.85 (0.19) | 68.37 (15.54) |
| Psoriasis (Balogh et al., 2014) | 200 | 32.00% | 50.66 (12.93) | 20.00% | 34.50% | 21.44 (11.69) | 0.69 (0.31) | 64.43 (21.34) |
| Psoriatic arthritis (Brodszky et al., 2009) | 183 | 57.38% | 50.15 (12.92) | 23.63% | 20.22% | 9.24 (9.24) | 0.47 (0.35) | 54.68 (20.01) |
| Bladder cancer (Hever et al., 2015) | 151 | 35.10% | 66.25 (9.58) | 18.79% | NA | 3.57 (3.74) | 0.79 (0.24) | 67.80 (19.34) |
| Age-related macular degeneration (Péntek et al., 2012a) | 122 | 62.30% | 75.16 (7.88) | 25.62% | 35.54% | 2.94 (2.54) | 0.66 (0.33) | 58.59 (16.43) |
| Parkinson's disease (Tamás et al., 2014) | 110 | 34.29% | 63.28 (11.26) | 36.36% | 21.70% | 8.22 (5.78) | 0.59 (0.28) | 59.32 (17.92) |
| Epilepsy (Pentek et al., 2013) | 100 | 58.00% | 36.65 (12.49) | 18.00% | 47.00% | 15.45 (12.12) | 0.80 (0.29) | 73.84 (15.85) |
| Dementia (Érsek et al., 2010) | 88 | 59.77% | 77.55 (8.52) | 13.64% | 18.60% | NA | 0.39 (0.33) | 48.59 (23.87) |
| Endometriosis (Simoens et al., 2012) | 84 | 100% | 32.80 (4.73) | 55.95% | 14.29% | 8.00 (6.46) | 0.90 (0.12) | NA |
| Systemic sclerosis (Minier et al., 2010) | 80 | 90.00% | 57.39 (9.60) | 20.00% | 27.50% | 7.16 (6.63) | 0.58 (0.29) | 56.25 (18.73) |
| Schizophrenia (Gulácsi et al., 2012) | 78 | 46.15% | 44.24 (13.05) | 11.54% | NA | NA | 0.64 (0.29) | 60.01 (24.71) |
| Multiple sclerosis (Péntek et al., 2012b) | 68 | 70.59% | 37.96 (9.08) | 41.79% | NA | 7.02 (5.90) | 0.67 (0.28) | 64.47 (22.18) |

NA: not available

More than half (59.9%) of the osteoporosis shad fractures, and 4.3% had femoral fractures (Péntek et al., 2016b). In benign prostatic hyperplasia the average International Prostate Symptom Score was 12.8 (SD=6.3) (Rencz et al., 2015c).

The proportion of those receiving biologic therapy at the time of the survey was 83.6% in macular degeneration in old age, 51.5% in psoriasis, 6.0% in AP, and 0% in RA (Péntek et al., 2012a, Brodszky et al., 2009, Péntek et al., 2007, Balogh et al., 2014). In the bladder cancer group, 13.2% of patients underwent cystectomy and 2.0% received palliative therapy only (Hever et al., 2015). Almost one half (45.5%) of the Parkinson's disease group belonged to categories I-II of the Hoehn & Yahr scale, which measures the severity of the disease (Tamás et al., 2014). The majority (60.8%) of the epilepsy group had seizures in the 12 months prior to the survey (Pentek et al., 2013). The mean Mini Mental Test value for patients with dementia was 16.70 (SD = 7.24)(Érsek et al., 2010). In systemic sclerosis, the proportion of diffuse cutaneous subgroup was 25.0% (Minier et al., 2010). In endometriosis, 26.2% of patients were treated surgically (Simoens et al., 2012). In schizophrenia, 39.7% of patients were in the more than moderate category as measured by the Global Clinical Scale (Gulácsi et al., 2012). The mean value of the Expanded Disability Status Scale in multiple sclerosis was 1.9 (SD 1.7) (Péntek et al., 2012b).

6.1.4.2. Informal care use

A quarter (27.4%) the of patients indicated that they had received informal care, with rates ranging from 6.5% (benign prostatic hyperplasia) to 87.2% (dementia) in various diseases. More than one-third of patients received informal care for dementia (87.2%), rheumatoid arthritis (49.8%), systemic sclerosis (38.8%), psoriatic arthritis (37.7%) and multiple sclerosis (36.8%). (Figure 10.)

**Figure 10. The rate of patients receiving informal care (%) by diagnosis and age**
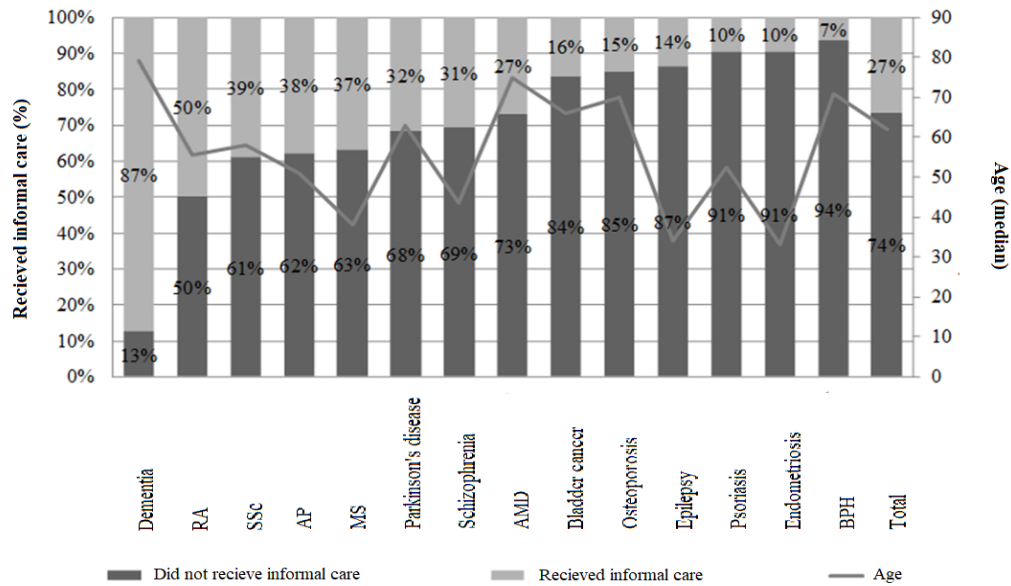


RA: rheumatoid arthritis, SSc: systemic sclerosis, AP: psoriatic arthritis, SM: multiple sclerosis, AMD: age-related macular degeneration, BPH: benign prostatic hyperplasia

The average number of hours of informal care per week per illness is presented in Figure 11. In our analysis (using a 24-hour / day limit), the average weekly number of hours in the total sample was 7.54 (SD = 26.36) hours. In only three diseases did the average duration of informal care exceed 10 hours per week, with a typically large variance (hours / week): dementia (72.19, SD = 69.56), multiple sclerosis (18.79, SD = 35.47) and Parkinson's disease (12.57, SD = 31.45). The lowest weekly informal care time was observed in endometriosis, psoriasis and benign prostatic hyperplasia, with an average of less than 2 hours per week in all three cases (1.20, SD = 5.05; 1.36, SD = 12.11; and 1, respectively). 51, SD = 7.18 hours / week). Based on the results of the Kruskal-Wallis test, the differences between the groups are significant (p = 0.000).

In our secondary analysis (using an 8-hour limit per day), informal care averaged 4.83 hours per week (SD = 12.2 hours), with the mean number of hours in dementia and epilepsy decreasing the most compared to the primary analysis. (Figure 11) For both approaches, the average was above 5 hours / week in dementia, SM, Parkinson's disease, RA, SSc, and AP. Based on the results of the Kruskal-Wallis test, the differences between the groups are also significant (p = 0.000).

**Figure 11. Average time of informal care received per diagnosis (hours / week), using a limit of 24 or 8 hours per patient per day**
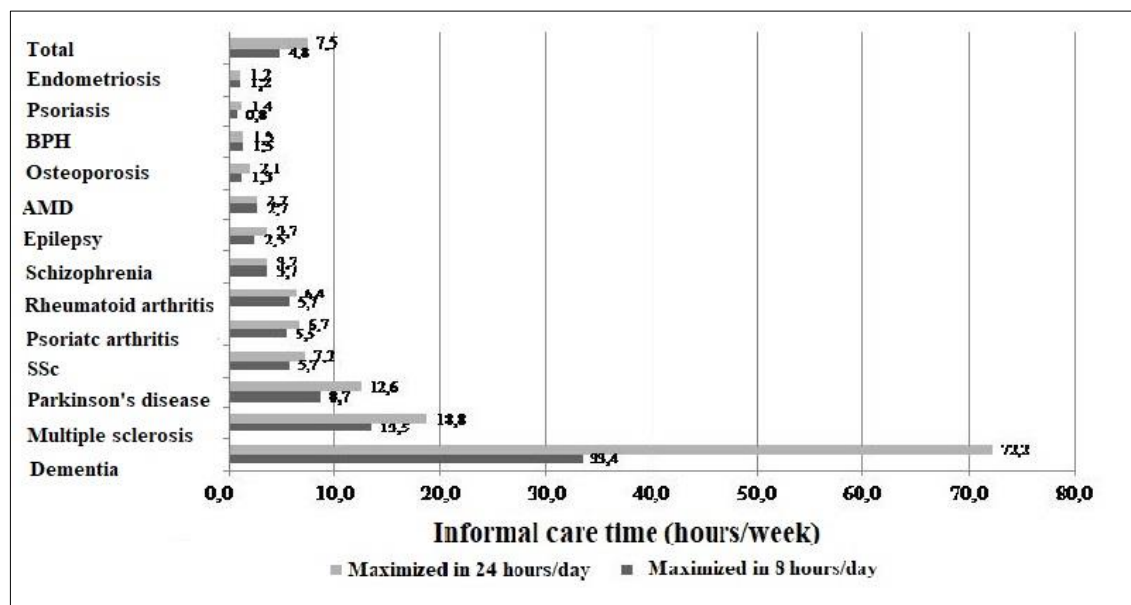


SSc: systemic sclerosis, AMD: age-related macular degeneration, BPH: benign prostatic hyperplasia

6.1.4.3. Patients' health status measured by the EQ-5D-3L questionnaire

Looking at the overall sample, most patients indicated that they had some or severe problems in the Pain / discomfort, Mobility, and Anxiety / Depression dimensions (62.8%, 52.9%, 51.7%, respectively), of which severe the proportion of those reporting a severe problem was 10.7%, 0.7% and 7.3%, respectively. In the Self-care and Usual activities dimensions, 74.8% and 53.3% of patients indicated that they had no problem, respectively. In the Mobility dimension, RA, Parkinson's disease and AP patient groups had the highest rates of problems (82.2%, 81.9%, 79.9%, respectively) and also in the Self-care dimension (52.3%, 55.3%, and 48.9%). In the Usual activities dimension, patients suffering from SSc, AP, and RA reported the most problems (77.9%, 77.5%, 75.8%, respectively). Pain / discomfort problems occurred at the highest rates in the RA, AP, and osteoporosis (91.9%, 90.6%, 87.7%, respectively), while problems in Anxiety / depression were most common in schizophrenia, SSc, and Parkinson's disease (76.9%, 70.0% and 68.3%).

6.1.4.4. Comparison of informal care recipients and non-recipients

Patients receiving informal care were on average 3.7 years older than those not receiving informal care. Approximately one-fifth (19.9%) of male patients received informal care, and almost one-third of women (32.5%). A slightly smaller proportion of patients living with family used informal care than people living alone (70.9% versus 75.6%). Regarding level of education, the share of those with primary or lower education was the highest, while the share of those with higher education was the lowest among those who received informal care (41.9% and 22.8%, respectively). (Table 9.)

**Table 8. Demographic characteristics of groups based of informal care use**

| Variables | Received informal care mean (SD) / n (%) | Did not receive informal care mean (SD) / n (%) |
|---|---|---|
| Number of patients | 1480 | 558 |
| Age | 57.88 (16.46) | 61.58 (15.60) |
| **Gender** | | |
| Women | 797 (53.9%) | 384 (69.4%) |
| Men | 682 (46.1%) | 169 (30.6%) |
| **Living conditions** | | |
| Living alone | 411 (32.8%) | 133 (27.8%) |
| Living with family | 841 (67.2%) | 346 (72.2%) |
| Disease duration (years) | 8.76 (9.15) | 9.52 (9.23) |
| **Education** | | |
| Lower than primary | 5 (0.4%) | 4 (0.7%) |
| Primary | 275 (23.2%) | 198 (36.7%) |
| Specialized school | 35 (3.0%) | 12 (2.2%) |
| Secondary | 557 (47.0%) | 233 (43.2%) |
| Higher | 312 (26.4%) | 92 (17.1%) |
| EQ-5D-3L index (-0,594 – 1) | 0.73 (0.27) | 0.42 (0.35) |
| EQ VAS (0 - 100) | 65.03 (18.71) | 49.29 (19.56) |

The average disease duration was 0.76 years longer for those receiving informal care than for those not receiving informal care, however the difference was not significant ($p = 0.066$). In all five dimensions of the EQ-5D-3L, the proportion of those who reported some or severe problems was higher among those receiving informal care than those who did not receive informal care. (Figure 12) The largest differences were in the Usual activities and Self-care dimensions (48.2% and 44.8%, respectively). To compare the health status of the two groups measured by the EQ-5D-3L index and EQ VAS, the Mann-Whitney U test was used; 0.000). The average informal care time of the subgroup receiving informal care is shown in Figure 13. (Figure 13.)

**Figure 12. Problems reported (%) in each EQ-5D-3L dimension**
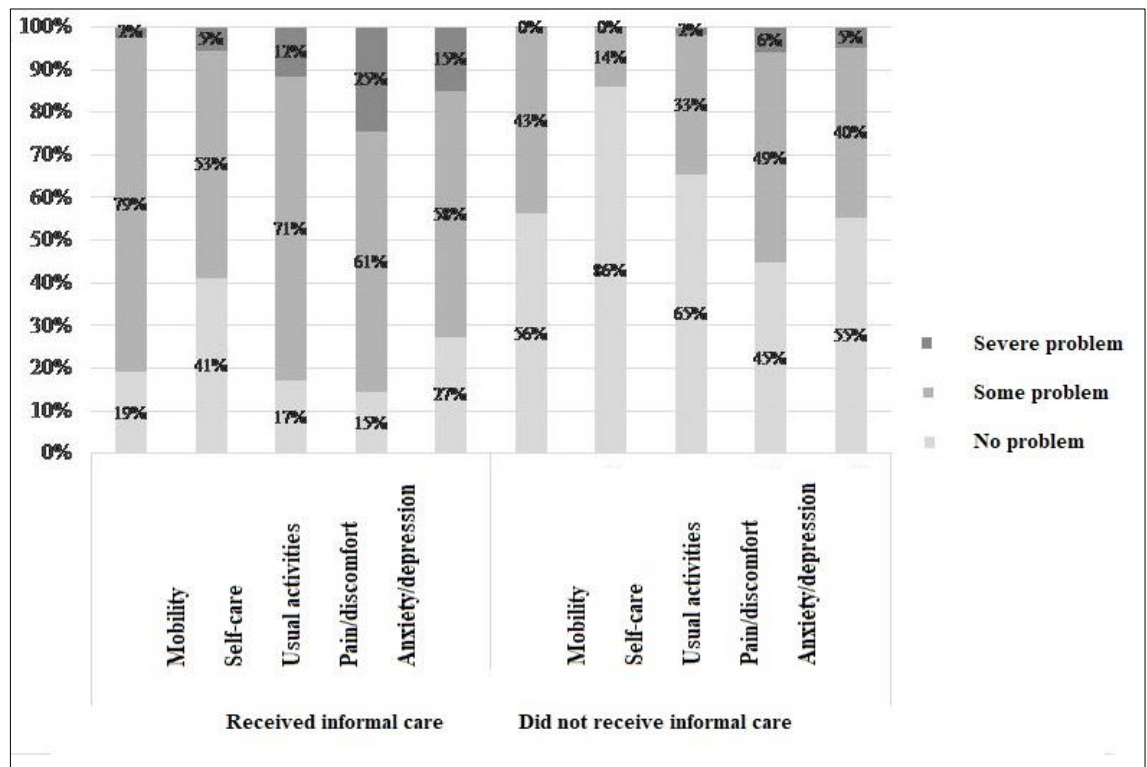
**Figure 13. Average time of informal care (hours / week), using a limit of 8 or 24 hours per patient per day (informal care recipients)**
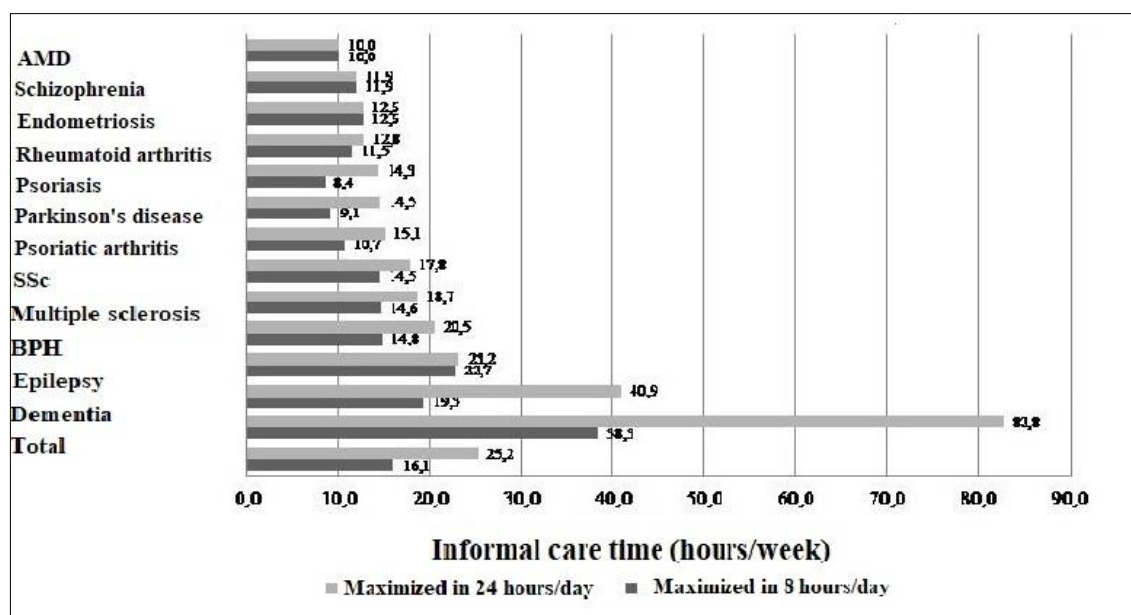


SSc: systemic sclerosis, AMD: age-related macular degeneration, BPH: benign prostatic hyperplasia

To explore the relationship between informal care time and patients' quality of life, we calculated Spearman's rank correlations. In the case of the EQ-5D-3L index and the EQ VAS, there was a negative, significant, but weaker-than-average relationship with the number of hours of informal care per week (r = -0.415, p = 0.000, and r = -0.328, p = 0.000).

6.1.4.5. Determinants of the informal care time

A linear regression model was constructed to explore the factors explaining the weekly received informal care time. In our model variables expressing patients' health status, demographics, and diagnosis dummy variables (in our model, the variable expressing RA was the basis for comparison) were included as explanatory variables. The EQ-5D-3L index (p = 0.002), EQ VAS (p = 0.000), gender (p = 0.044), and osteoporosis (p = 0.011) and Parkinson's disease (p = 0.011) variables were significant. (Table 10) In the model, the value of the $R^2$ was 0.062.

If the maximum informal care time (hours / week) limited in 8 hours a day was considered as the outcome variable, the explanatory variables were age (p = 0.017), gender (p = 0.016), EQ VAS (p = 0.000), EQ-5D-3L index (p = 0.000) and dummy variables expressing the presence of some diseases were significant (Parkinson's disease p = 0.009; osteoporosis p = 0.000; age-related macular degeneration p = 0.021; psoriasis p = 0.029). In our model, the value of the $R^2$ in this case was 0.111, that is, we can only estimate to a very limited extent the value of informal care used based on the explanatory variables we used. (Table 10.)

**Table 9. Linear regression model: informal care time (hours/week)**

| Variables | Non-standardized coefficients | | Standardized coefficients | t | Significance |
|---|---|---|---|---|---|
| | B | Std. error | Beta | | |
| Constant | 7.909 | 3.088 | - | 2.562 | 0.011 |
| Age | 0.060 | 0.041 | 0.057 | 1.477 | 0.140 |
| Disease duration | 0.027 | 0.054 | 0.016 | 0.505 | 0.613 |
| Gender | 2.371 | 1.174 | 0.072 | 2.020 | 0.044 |
| EQ VAS | -0.091 | 0.025 | -0.110 | -3.615 | 0.000 |
| EQ-5D | -4.840 | 1.543 | -0.098 | -3.138 | 0.002 |
| Psoriatic arthritis | 1.434 | 1.655 | 0.029 | 0.866 | 0.386 |
| Psoriasis | -1.641 | 1.892 | -0.034 | -0.867 | 0.386 |
| Age-related macular degeneration | -2.723 | 2.067 | -0.047 | -1.318 | 0.188 |
| Systemic sclerosis | 1.468 | 2.065 | 0.021 | 0.711 | 0.477 |
| Osteoporosis | -4.293 | 1.691 | -0.091 | -2.538 | 0.011 |
| Benign prostatic hyperplasia | -0.281 | 2.031 | -0.006 | -0.138 | 0.890 |
| Epilepsy | 4.160 | 2.197 | 0.065 | 1.893 | 0.059 |
| Parkinson's disease | 5.514 | 2.155 | 0.081 | 2.558 | 0.011 |

Coding: men=0, women=1; diagnoses: 0=no, 1=yes

## 6.2. Costing

## 6.2.1. Cost of informal care in chronic diseases in Hungary: A comparative analysis

A total of 1,896 patients were enrolled in the 13 studies included in our analysis, with a mean age of 58.29 (SD = 16.62) years, of whom 59.9% were female, with a mean age of 57.45 (SD 16.98) years. and 59.51 (SD = 16.01) years for men. The studies covered both major, high-prevalence diseases and less common diseases, with the three largest patients being osteoporosis (n = 282), RA (N = 255), and benign prostatic hyperplasia (N = 246). Patients had a mean EQ-5D-3L index of 0.629 (SD = 0.331) and a median = 0.725, with a mean EQ VAS of 59.87 (SD = 20.21) with a median of 60.

A quarter (27.4%) of the patients received informal care, ranging from 6.5% (benign prostatic hyperplasia) to 87.2% (dementia) in various diseases. More than one-third of patients received informal care in dementia (87.2%), rheumatoid arthritis (49.8%), systemic sclerosis (38.8%), psoriatic arthritis (37.7%), and multiple sclerosis (36.8%).

### 6.2.1.1. Informal care use of patients who reported a problem in the EQ-5D-3L dimensions

The average informal care time of those patients, who reported some problems in the Self-care dimension using a 24-hour limit was 8.13 (SD = 16.95) hours / week, and with an 8-hour limit it was 7.33 (SD = 11.42) hours / week. 15.9% of those not receiving informal care reported some problems in this dimension. It important to mention the in the Mobility, Self-care and Usual activities dimensions the average informal care time per week of is extremely high for those who indicate a serious problem. (Table 11.)

**Table 10. Problems reported in the EQ-5D-3L dimension and informal care use**

| EQ-5D dimension | Patients who received informal care Weekly informal care time mean (SD) | | Patients who did not receive informal care (%) |
| --- | --- | --- | --- |
| | Maximized in weekly 56 hours | Maximized in weekly 168 hours | |
| **Mobility** | | | |
| No problem | 1.36 (6.32) | 1.74 (10.42) | 54.30% |
| Some problem | 5.10 (10.78) | 6.55 (20.35) | 45.40% |
| Confined to bed | 14.62 (16.81) | 23.23 (44.94) | 0.30% |
| **Self-care** | | | |
| No problem | 1.73 (6.91) | 2.38 (13.36) | 83.40% |
| Some problem | 7.33 (11.42) | 8.13 (16.95) | 15.90% |
| Unable | 19.28 (20.89) | 34.86 (56.24) | 0.60% |
| **Usual activities** | | | |
| No problem | 1.13 (5.90) | 1.60 (11.27) | 62.60% |
| Some problem | 5.37 (10.65) | 6.50 (18.53) | 35.20% |
| Unable | 11.58 (16.18) | 17.69 (38.23) | 2.20% |
| **Pain/discomfort** | | | |
| No | 1.85 (7.69) | 2.29 11.86) | 41.60% |
| Moderate | 3.73 (9.43) | 4.74 (17.21) | 51.20% |
| Extreme | 7.42 (11.95) | 10.24 (26.80) | 7.30% |
| **Anxiety/depression** | | | |
| No | 1.79 (6.73) | 2.18 (10.98) | 54.40% |
| Moderate | 4.71 (10.98) | 6.41 (21.64) | 40.60% |
| Extreme | 6.97 (10.81) | 7.89(17.62) | 5.00% |

6.2.1.2. Informal care use of the patients in the worst health states

To identify patients with the worst health condition, we examined patients who had an EQ-5D-3L index value of 0 or lower, and 162 (9.1%) such patients were identified. Of whom, 26.1% had rheumatoid arthritis, 17.6% psoriatic arthritis, 13.9% dementia, and 13.3% had osteoporosis. In endometriosis, there were no patients with an EQ-5D-3L of 0 or lower. The mean age of those with the worst health status was 62.1 years (SD = 14.6 years) and 66% were female. A third (31%) of those patients who had an EQ-5D-3L index value of 0 or lower lived alone.

Regarding informal care, 51 (31.5%) of those with the worst health status did not receive informal care and 15 of them lived alone. The average of informal care time was 18.71 hours/week (SD = 39.43) using the 24-hour limit and 11.65 hour/week (SD = 16.79) using the 8-hour limit. The highest average weekly informal care time was observed in this case in dementia and Parkinson's disease. Compared to those with an EQ-5D-3L index value higher than 0, the average number of hours of informal care for those in the worst health is higher in all diagnoses. (Table 12)

**Table 11. Patients in the worst health states (N=165) by diagnosis***

| Diagnosis | Informal care time hours/patient mean (SD) | | | |
| --- | --- | --- | --- | --- |
| | Patients in the worst health states ** | | Patients with an EQ-5D-3L index score higher than 0 | |
| | Maximized in weekly 56 hours | Maximized in weekly 168 hours | Maximized in weekly 56 hours | Maximized in weekly 168 hours |
| Psoriatic arthritis | 10.72 (9.98) | 10.72 (9.98) | 4.52 (10.53) | 6.03 (20.88) |
| Psoriasis | 11.52 (17.93) | 22.72 (51.80) | 0.25 (1.09) | 0.25 (1.09) |
| Age-related macular degeneration | 1.33 (2.65) | 1.33 (2.65) | 2.83 (8.26) | 2.83 (8.26) |
| Rheumatoid arthritis | 8.02 (11.51) | 8.99 (16.42) | 5.35 (9.78) | 5.93 (14.08) |
| Systemic sclerosis | 2.33 (4.04) | 2.33 (4.04) | 5.79 (12.34) | 7.42 (21.99) |
| Dementia | 39.63 (19.71) | 79.21 (64.09) | 31.21 (24.82) | 69.77 (71.67) |
| Osteoporosis | 4.77 (7.31) | 4.77 (7.31) | 1.07 (4.85) | 1.68 (12.61) |
| Benign prostatic hyperplasia | 0*** | 0*** | 1.54 (7.05) | 1.57 (7.32) |
| Epilepsy | 1.86 (2.73) | 1.86 (2.73) | 2.56 (10.34) | 5.57 (27.02) |
| Parkinson's disease | 6.33 (18.63) | 18.78 (55.96) | 8.87 (15.58) | 12.07 (29.58) |
| Schizophrenia | 6.8 (9.55) | 6.8 (9.55) | 3.44 (6.64) | 3.44 (6.64) |
| Multiple sclerosis | 5*** | 5*** | 13.91 (16.63) | 19.39 (36.15) |

*In endometriosis, there were no patients whose EQ-5D-3L index score was lower than or equal to 0
**EQ-5D-3L index score lower than or equal to 0
***N=1

6.2.1.3. The cost of informal care

The weekly cost of informal care in our entire sample, using the 24-hour limit, was on average 7,399 HUF (SD = 25,648) and using the 8-hour limit per day, it was 4,696 HUF (SD = 11828) per patient. Based on the results of the Kruslkal-Wallis test, the costs differ significantly in different diagnoses according to both our primary and secondary analysis (p <0.001 in both cases). (Table 13.)

**Table 12. Informal care costs (HUF/patient/week) by diagnosis**

| Diagnosis | Number of patients (n) | Received informal care (%) | Informal care recipients Informal care cost hours/patient mean (SD) | |
|---|---|---|---|---|
| | | | Maximized in weekly 56 hours | Maximized in weekly 168 hours |
| Psoriatic arthritis | 183 | 37.7% | 14130 (12527) | 17288 (27474) |
| Psoriasis | 200 | 9.5% | 8204 (12756) | 13939 (36718) |
| Age-related macular degeneration | 122 | 27.9% | 9752 (12520) | 9752 (12520) |
| Rheumatoid arthritis | 255 | 49.8% | 11168 (11350) | 12401 (17787) |
| Systemic sclerosis | 80 | 38.8% | 14203 (15489) | 18157 (30904) |
| Dementia | 86 | 87.2% | 37218 (20899) | 80530 (66503) |
| Endometriosis | 84 | 9.5% | 12223 (11470) | 12223 (11470) |
| Osteoporosis | 281 | 14.9% | 8816 (11882) | 14132 (34695) |
| Benign prostatic hyperplasia | 246 | 6.5% | 22075 (15920) | 22561 (16995) |
| Epilepsy | 100 | 13.5% | 18876 (21152) | 39743 (61801) |
| Parkinson's disease | 109 | 31.8% | 10376 (16208) | 14642 (33074) |
| Schizophrenia | 78 | 30.8% | 11554 (7181) | 11554 (7181) |
| Multiple sclerosis | 24 | 36.8% | 14374 (16120) | 19947 (35678) |

The average cost of informal care was higher for female patients than for male patients, including the 24- and 8-hour limits: 4004 (SD = 11617) and 5144 (SD = 11971) and 6827 (SD = 26522) and 7680 (SD = 25116) forint. Based on the results of the Mann-Whitney U test, the difference is significant in both cases (p <0.001 in both cases).

The cost of informal care for informal care users alone was average 24,509 HUF (SD = 42,281) per week, using the 24-hour limit, and 1,5,646 HUF (SD = 17,100) using the 8-hour limit per day. The highest cost is in dementia (using a 24-hour limit of 80530 HUF / patient / week and with an 8-hour limit of 37218 HUF / patient / week), the lowest cost was found in age -related macular degeneration (9752 HUF / patient / week) and endometriosis (12223 HUF / patient / week). However, the lowest cost using the 8-hour limit was observed in the case of psoriasis (8204 (SD = 12756) HUF / patient / week). (Table 13.) No significant difference by gender was found based on the results of the Mann-Whitney U test (p = 0.346 and p = 0.383).

6.2.1.4. The determinants of informal care cost

To explore the relationship between the variables, we calculated pairwise Spearman's rank correlations. A weaker than average negative relationship was observed between the cost of weekly informal care and the EQ-5D-3L index expressing patients' quality of life ($r = -0.415$, $p < 0.001$) and the EQ VAS value ($r = -0.326$, $p < 0.001$), indicating that patients in a worse condition received more informal care. We found an extremely weak but significant correlation between the cost of informal care and age ($r = 0.094$, $p < 0.001$), indicating that older patients received more informal care than younger ones.

6.2.1.5. The yearly costs of informal care

Table 14 shows the informal cost per patient per year for each disease, calculated with the 8-hour informal care time limit providing a more conservative estimate. The average annual costs per patient ranged from 125,635 HUF (psoriasis) to 5,233,482 HUF (dementia). (Table 14.)

**Table 13. Estimated informal care cost/patient/year (HUF) in Hungary**

| Diagnosis | Prevalence in Hungary | Estimated number of patients in Hungary | Estimated informal care cost/year/patient (HUF) |
|---|---|---|---|
| Psoriatic arthritis | 0,1-0,3% (Brodszky et al., 2009, Brodszky et al., 2010d) | 20 000 | 858805 |
| Psoriasis | 0,73-2,9% (OEP, 2009, Balogh et al., 2014, Herszényi et al., Rencz et al., 2015b) | 181 500 | 125635 |
| Age-related macular degeneration | 0,1%-9,8% (Péntek et al., 2017a, Colijn et al., 2017) | 115 390 | 426510 |
| Rheumatoid arthritis | 0,5% (Herszényi et al., Kiss et al., 2005, Lepp-Gazdag et al., 2002, Péntek et al., 2007, Dorner et al., 2016) | 50 000 | 896645 |
| Systemic sclerosis | 0,7-48, 9/100 000 (Minier et al., 2010) | 24 800 | 887169 |
| Dementia | 1316/100 000 (Érsek et al., 2010) | 131 995 | 5233482 |
| Endometriosis | 2-10% (Simoens et al., 2012) | 600 000 | 187657 |
| Osteoporosis | 2,5-21,2%* (Hernlund et al., 2013, Raspe et al., 1998) | 600 000 women and 300 000 men* (OEP, 2013) | 207363 |
| Benign prostatic hyperplasia | 8-90%-a*** (Rencz, 2012) | 415 000 (Rencz et al., 2015c) | 231446 |
| Epilepsy | 0,3-0,6% (EMMI, 2017, Pentek et al., 2013) | 45 000 | 393687 |
| Parkinson's disease | 100-200/100 000 (OEP, 2013, Olesen et al., 2012, Tamás et al., 2014) | 20 000 (Tamás et al., 2014) | 1366661 |
| Schizophrenia | 1% (OEP, 2010b) | 100 000 | 573097 |
| Multiple sclerosis | 25-224/100 000(OEP, 2010a) | 7000 | 2123978 |

*Different prevalence based on gender and age

**In our sample, 60% of the patients suffering from osteoporosis had a fracture

***Prevalence: age 31-40: 8%, age 41-50: 20%, age 51-60: 50%, age 61-70: 70%, age 71-80: 80%, ages over: 80% of the male population

### 6.2.2. Cost-of-illness studies in nine Central and Eastern European countries

6.2.2.1. Selection of the publications

After excluding duplicates (n = 246), our search resulted in 607 potentially relevant publications, of which 55 were not fully available and a further 98 reviews were available. A further 282 publications did not include cost of illness data, 54 did not focus on the cost of a specific disease, and 67 reports reported the cost of a therapy/intervention. A total of 50 studies matched our selection criteria from database search results.

As a result of an additional search for local literature, 8 more articles were selected (Austria: n = 2, Bulgaria: n = 5, Hungary: n = 1). A total of 58 publications (sometimes covering results for several countries) were selected: Hungary (n = 24), Bulgaria (n = 16), Poland (n = 11), Czech Republic (n = 10), Austria (n = 9), Slovenia (n = 4), Croatia (n = 3), Slovakia (n = 3) and Romania (n = 3).

6.2.2.2. Characteristics of selected publications

The majority of selected papers included results for one country (74%), however, 15 studies reported results for more than one country, for a total of 83 country-specific results for the 58 selected papers. Three quarters of the publications were in English (n = 44) and except for 5 publications (Georgieva, 2015, Glogovska et al., 2010, Ivanova et al., 2014, Kyuchukov et al., 2015, Todorova, 2007) an English abstract was available for all non-English language publications. The majority of publications reported costs in euros (n = 45, 78%). A total of 37 publications converted the local currency into euros, of which 17 (46%) provided the exchange rate, 5 (14%) the source of the exchange rate, and 15 (40%) publications did not provide information on the conversion at all. The reporting of cost data in local currency was the most common in Romania (67%). A total of 47 (81%) publications reported information on research funding. The lack of funding was most common in Romania (n = 2.67%) and Bulgaria (n = 5; 31%).

By clinical area, "Endocrine, nutritional, and metabolic diseases" were the most common in the publications (n = 15 country-specific results), followed by "Neoplasms" (n = 12),

and "Certain infectious and parasitic diseases" (n = 10). (Figure 14.) A total of 48 different diseases were analysed in the 58 selected papers.

**Figure 14. Distribution of COI studies by ICD classification**
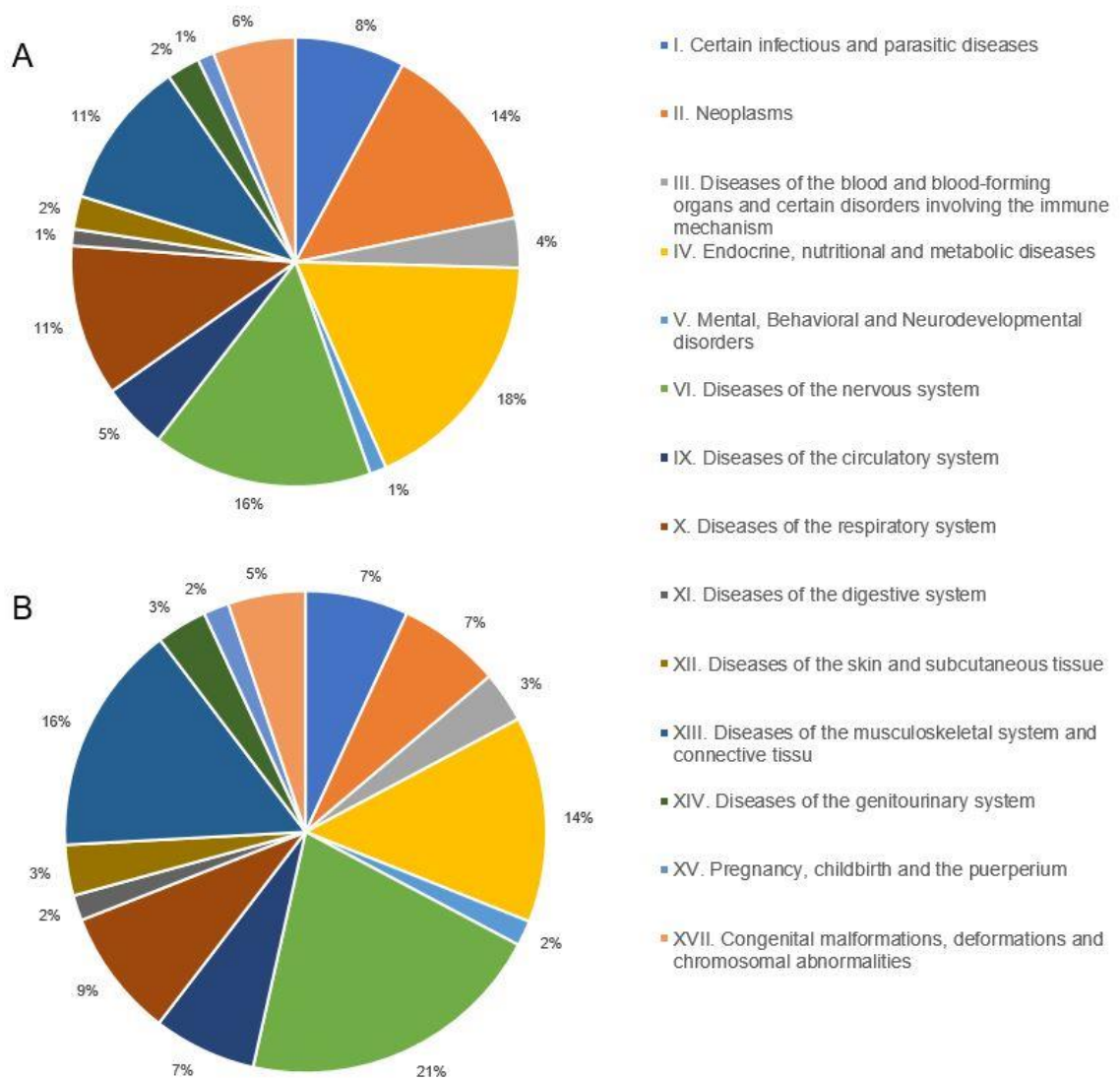


A: Distribution of country-specific results across clinical areas defined by ICD groups (n=83)
B: Distribution of studies between clinical areas defined by ICD groups (n=58)

6.2.2.3. Methods used in the selected publications

The characteristics by country are summarized in Table 15. The data were mostly from retrospective, self-administered questionnaires (48%), followed by retrospective "claims data" analysis (14%) and prospective surveys (14%). Sample sizes ranged from n = 2

(small cohorts) to n = 127,512 (large population surveys). Of the 58 studies selected, 26 (45%) reported aggregate results in all major cost categories (direct health, direct non-health, and indirect costs).

The majority of the selected research used a social perspective (52%) and 17% conducted the analysis from the perspective of the financer. In the publications where it was reported, bottom-up (38%) and top-down (21%) methods were most commonly used. Data on productivity loss were reported in 47 (81%) publications. The human capital (72%) and friction cost (23%) methods were most commonly used to assess productivity loss. More than half (58%) of the publications did not report unit costs at all. (Table 15.)

**Table 14. Characteristics of cost-of-illness studies**

| | Austria[1] | Bulgaria[2] | Croatia[3] | Czech Republic[4] | Hungary[5] | Poland[6] | Romania[7] | Slovakia[8] | Slovenia[9] | Total |
|---|---|---|---|---|---|---|---|---|---|---|
| **Number of country specific results: N=83; Number of papers: N=58** | | | | | | | | | | |
| **Number of publications** | 9 | 16 | 3 | 10 | 24 | 11 | 3 | 3 | 4 | 58 |
| English language | 5 | 11 | 3 | 10 | 21 | 11 | 1 | 3 | 4 | 44 |
| Local language | 4 | 5 | 0 | 0 | 3 | 0 | 2 | 0 | 0 | 14 |
| **Search** | | | | | | | | | | |
| Electronic database | 7 | 11 | 3 | 10 | 23 | 11 | 3 | 3 | 3 | 50 |
| Hand search | 2 | 5 | NA | NA | 1 | NA | NA | NA | NA | 8 |
| **Currency** | | | | | | | | | | |
| Euro | 9 | 10 | 3 | 10 | 21 | 10 | 1 | 3 | 3 | 45 |
| National currency | NA | 6 | 0 | 0 | 3 | 1 | 2 | 0 | 1 | 13 |
| **Data source** | | | | | | | | | | |
| Cross-sectional questionnaire | 6 | 9 | 0 | 3 | 15 | 1 | 0 | 0 | 0 | 28 |
| Retrospective chart review | 1 | 1 | 0 | 2 | 2 | 1 | 0 | 1 | 0 | 5 |
| Interview-based, prospective | 3 | 2 | 0 | 1 | 0 | 3 | 1 | 0 | 0 | 8 |
| Retrospective claims data | 0 | 0 | 0 | 1 | 5 | 3 | 1 | 1 | 0 | 8 |
| Multiple source | 1 | 2 | 1 | 2 | 1 | 2 | 1 | 1 | 3 | 6 |
| Modelling | 0 | 1 | 2 | 1 | 1 | 1 | 0 | 0 | 1 | 2 |
| NR | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | NR 0 | 1 |
| **Perspective** | | | | | | | | | | |
| Payer | 2 | 2 | 2 | 2 | 2 | 3 | 0 | 1 | 2 | 10 |
| Societal | 2 | 8 | 0 | 3 | 18 | 4 | 0 | 0 | 1 | 30 |
| Patient | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 |
| Hospital | 0 | 5 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 6 |
| NR | 5 | 1 | 1 | 5 | 4 | 4 | 2 | 2 | 1 | 13 |
| **Costing** | | | | | | | | | | |
| Top-down | 1 | 1 | 0 | 1 | 1 | 2 | 0 | 1 | 0 | 12 |
| Bottom-up | 3 | 10 | 1 | 3 | 16 | 2 | 0 | 1 | 2 | 22 |
| NR | 5 | 5 | 2 | 6 | 7 | 7 | 3 | 1 | 2 | 24 |

| | Austria[1] | Bulgaria[2] | Croatia[3] | Czech Republic[4] | Hungary[5] | Poland[6] | Romania[7] | Slovakia[8] | Slovenia[9] | Total |
|---|---|---|---|---|---|---|---|---|---|---|
| **Methods of estimating indirect cost** | | | | | | | | | | |
| Human capital | 5 | 8 | 0 | 3 | 18 | 7 | 0 | 1 | 1 | 34 |
| Friction cost | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 1 | 1 | 11 |
| NR | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 2 |
| N/A | 3 | 7 | 2 | 5 | 2 | 3 | 2 | 1 | 2 | 11 |
| **Informal care costs** | | | | | | | | | | |
| Market price | 0 | 8 | 1 | 0 | 16 | 1 | 0 | 0 | 0 | 5 |
| Opportunity cost | 1 | 1 | 0 | 3 | 2 | 1 | 1 | 1 | 1 | 3 |
| NR | 2 | 0 | 0 | 2 | 0 | 1 | 0 | 0 | 0 | 20 |
| Other | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| N/A | 5 | 7 | 2 | 5 | 6 | 7 | 2 | 2 | 3 | 29 |
| **Funding** | | | | | | | | | | |
| EU | 1 | 8 | 0 | 0 | 9 | 1 | 0 | 0 | 0 | 13 |
| Pharmaceutical company | 5 | 2 | 1 | 3 | 8 | 4 | 1 | 3 | 1 | 11 |
| Government | 1 | 0 | 0 | 5 | 3 | 1 | 0 | 0 | 0 | 13 |
| Other | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 |
| No funding | 2 | 1 | 2 | 1 | 4 | 3 | 0 | 0 | 2 | 11 |
| NR | 1 | 5 | 0 | 0 | 0 | 3 | 2 | 0 | 1 | 11 |
| **Cost/patient** | | | | | | | | | | |
| Direct healthcare cost | 5 | 13 | 1 | 4 | 20 | 5 | 3 | 1 | 1 | 38 |
| Indirect | 6 | 10 | 2 | 6 | 21 | 9 | 1 | 2 | 3 | 38 |
| Informal care | 4 | 9 | 1 | 5 | 18 | 3 | 1 | 1 | 1 | 29 |
| Total | 8 | 13 | 3 | 7 | 23 | 9 | 3 | 3 | 3 | 47 |
| **Unit cost** | | | | | | | | | | |
| Reported | 3 | 8 | 1 | 7 | 16 | 5 | 2 | 1 | 2 | 24 |
| Not reported | 6 | 8 | 2 | 3 | 8 | 6 | 1 | 2 | 2 | 34 |

NA: not available, NR:not-reported,[1](Grabmeier-Pfistershammer et al., 2013, Kobelt et al., 2006, Leal et al., 2016, Prast et al., 2013, von Campenhausen et al., 2009, Willich et al., 2006, Dimai et al., 2012, Wagner, 2011, Wagner, 2012); [2](Kuhlmann et al., 2016, Iskrov et al., 2015, Jakubczyk et al., 2016, Leal et al., 2016, Valov et al., 2014, Georgieva, 2015, Glogovska et al., 2010, Ivanova et al., 2014, Kyuchukov et al., 2015, Todorova, 2007, Angelis et al., 2016c, Péntek et al., 2016a, Chevreul et al., 2016a, Lopez-Bastida et al., 2016a, Lopez-Bastida et al., 2016b, Cavazza et al., 2016b); [3](Jakubczyk et al., 2016, Leal et al., 2016, Bauer et al., 2014); [4](Blahova Dusankova et al., 2012, Jakubczyk et al., 2016, Klimeš et al., 2014, Leal et al., 2016, Maresova et al., 2016, Mlcoch et al., 2017, Tichopad et al., 2016, Tichopad et al., 2013, Winter et al., 2010, Holmerova et al., 2016); [5](Brodszky et al., 2009, Gulácsi et al., 2007, Jakubczyk et al., 2016, Leal et al., 2016, Lopez-Bastida et al., 2016a, Minier et al., 2010, Péntek et al., 2012b, Rencz et al., 2015c, Tamás et al., 2014, Tichopad et al., 2016, Tichopad et al., 2013, Érsek et al., 2010, Péntek et al., 2007, Inotai et al., 2015, Lopez-Bastida et al., 2016b, Kuhlmann et al., 2016, Angelis et al., 2016c, Balogh et al., 2014, Pentek et al., 2013, Péntek et al., 2012c, Cavazza et al., 2016b, Péntek et al., 2012a); [6](Czech et al., 2013b, Dubas-Jakobczyk et al., 2016, Jakubczyk et al., 2016, Jaworski et al., 2012, Kawalec et al., 2015, Leal et al., 2016, Lesniowska et al., 2014, Szmurlo et al., 2014, Tichopad et al., 2016, Tichopad et al., 2013, Czech et al., 2013a); [7](Leal et al., 2016, Stoicescu et al., 2007, Stambu et al., 2013); [8](Leal et al., 2016, Tichopad et al., 2016, Tichopad et al., 2013); [9](Dzajkovska et al., 2007, Jakubczyk et al., 2016, Leal et al., 2016, Nerat et al., 2013)

6.2.2.4. Comparing the costs of seleted individual diseases

A total of 83 country-specific cost data were reported in selected publications, which included 48 different diseases. In addition to rare diseases, multiple sclerosis had the highest disease burden (average total cost per patient) in three countries (Austria 50,599 EUR, Czech Republic 14,777 EUR and Poland 12,343 EUR) (Blahova Dusankova et al., 2012, Kobelt et al., 2006, Szmurlo et al., 2014).

In Hungary, schizophrenia (15,187 EUR) and gestational diabetes (32,263 EUR) were the highest-cost diseases in Bulgaria (Todorova, 2007, Péntek et al., 2012c).

Multi-country research has been conducted in 9 diagnoses (rotavirus gastroenteritis, pneumonia, bladder cancer, hypoglycaemia, Duchenne muscular dystrophy, epidermolysis bullosa, Prader-Willi syndrome, cystic fibrosis, haemophilia). One study (bladder cancer) was included in the sample that reported results for all nine countries and an additional one (hypoglycaemia) for six countries. Two reports reported data for four different countries (rotavirus gastroenteritis and pneumonia)

In the bladder cancer research, which included results from nine countries, the methodologies used in each country varied, with an average cost of 7,421 EUR (with country averages ranging from 2,320 EUR (Bulgaria) to 16,479 EUR (Slovenia)). Hypoglycaemia research, which included six countries and had an average total cost per patient (11 EUR), ranged from 5 EUR (Bulgaria) to 18 EUR (Slovenia) (Jakubczyk et al., 2016).

Separate but identical disease research has been found in eight diagnoses: multiple sclerosis, dementia, Parkinson's disease, rheumatoid arthritis, osteoporosis, chronic obstructive pulmonary disease, systemic sclerosis, and diabetes.

The most commonly discussed diseases were multiple sclerosis and diabetes, each appearing in multiple (four) studies (Kobelt et al., 2006, Péntek et al., 2012b). In the case of diabetes, the highest direct cost was found in Hungary (1,309 EUR), and the lowest in Bulgaria (472 EUR) (Nerat et al., 2013, Valov et al., 2014).

### 6.2.3. Hungarian cost library

6.2.3.1.Characteristics of selected publications

Our **cost of illness** search resulted in 105 items of which 26 was included (Angelis et al., 2016b, Balogh et al., 2014, Brodszky et al., 2009, Chevreul et al., 2016a, Chevreul et al., 2016b, Érsek et al., 2010, Gulácsi et al., Inotai et al., 2015, Jakubczyk et al., 2016, Lopez-Bastida et al., 2016a, Lopez-Bastida et al., 2016b, Minier et al., 2010, Pentek et al., 2013, Péntek et al., 2016a, Péntek et al., 2012b, Péntek et al., 2012c, Péntek et al., 2007, Péntek et al., 2008, Rencz et al., 2015c, Tichopad et al., 2016, Tichopad et al., 2013, Horvath et al., 2014, Leal et al., 2016, Tamás et al., 2014, Angelis et al., 2016a). The **cost-effectiveness and budget-impact analysis** search resulted in 79 publications, of which we included 25 publications (Baji et al., 2012a, Baji et al., 2012b, Brodszky et al., 2014b, Dasbach et al., 2010, Iversen et al., 2015, Mandel et al., 2014, Marada et al., 2016, Nagy et al., 2014, Scuffham et al., 2006, Vokó et al., 2012, Zemplenyi et al., 2016, Boncz et al., 2010, Kovacs et al., 2014, Brodszky et al., 2010c, Daroczi et al., 2016). Altogether 13 health technology assessments were included as a result of our hand-search (Brodszky et al., 2006a, Brodszky et al., 2006b, Brodszky et al., 2007, Brodszky et al., 2010b, Gulácsi, 2010, Brodszky et al., 2010a, Brodszky et al., 2011a, Gulácsi et al., 2011, Brodszky et al., 2011b, Brodszky et al., 2011c, Brodszky et al., 2012, Brodszky et al., 2013, Brodszky et al., 2015{ ) along with seven additional Hungarian publications (Bodnár et al., 2010, Borsos et al., 2006, Brodszky et al., 2010e, Harangozó et al., 2008, József, 2006, Kárpáti et al., 2007, Kósa József et al., 2008). When updating our search, we found an additional 314 publications, of which 14 was included in our analysis (Brodszky et al., 2020, Fejes et al., 2019, Vallejo-Torres et al., 2018, Trapero-Bertran et al., 2018, Németh et al., 2018, Coyle et al., 2018, Bocskai et al., 2018, Baji et al., 2018, Rencz et al., 2017, Péntek et al., 2017b, Péntek et al., 2017c, Meszner et al., 2017, Kobelt et al., 2017, Brodszky et al., 2017).

The Hungarian cost library was created based on the 75 included publications. Out of the 75 publications, we managed to extract 1289 cost items. The majority of the studies included (56%, n=42) were cost of illness articles. Altogether 1 health technology reports and 13 cost-effectiveness studies were identified. We included one (1,3%) budget impact analysis (Brodszky et al., 2014b), one (1,3%) cost-utility analysis (Rencz et al., 2017) and one (1,3%) cost-minimization study (Kósa József et al., 2008) and 4 (5,3%) other

type of publications (Péntek et al., 2017c, Baji et al., 2012a, Baji et al., 2012b, Marada et al., 2016) in our analysis.

The distribution of selected publications by year of publication is shown in Figure 15. Most of the identified publications were found in 2016 (n = 14), followed by 2010 (n = 10) and 2014, (n = 7). Most of the identified publications in Hungarian were published in 2010 (n = 5). (Figure 15.)

**Figure 15. Publications included, by language and publication year (n)**
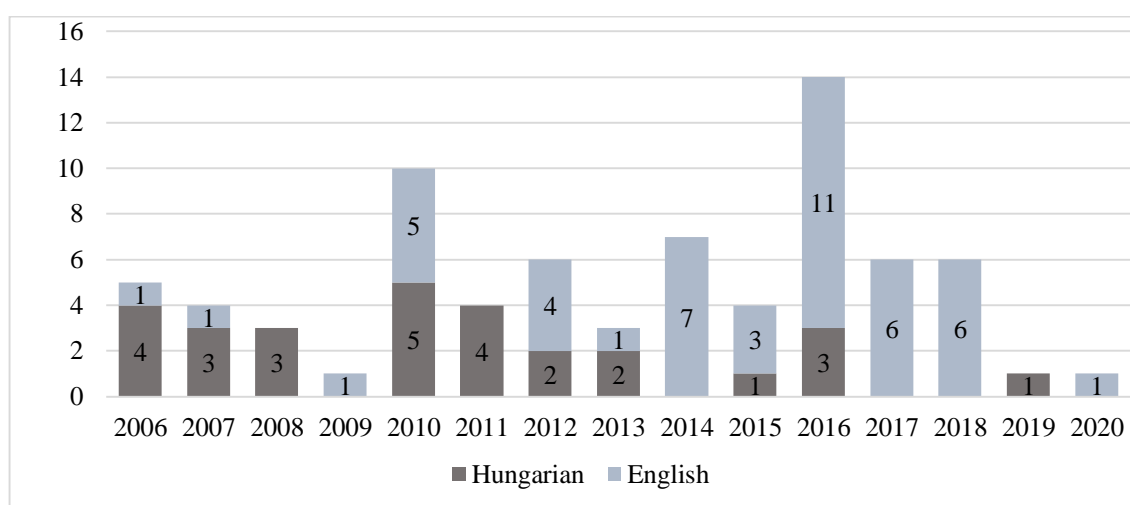


6.2.3.2.    Clinical areas

The selected publications covered a large number of different clinical areas. To cathegorise the publications, we used the International Statistical Classification of Diseases and Related Health Problems (ICD-10 Version: 16) to evaluate the diseases / interventions they contain (ICD, 2016). Four of the selected publications (6.3%) were not related to a specific ICD main group. These focused on informal payment (n=2) (Baji et al., 2012a, Baji et al., 2012b), different dental and oral surgeries (n=1) (Marada et al., 2016), and the costs of anaesthesia (n=1) (Bocskai et al., 2018).

The most common group was "Musculoskeletal and connective tissue disorders" (n=15, 20,0%) (Brodszky et al., 2010b, Brodszky et al., 2011a, Gulácsi et al., 2011, Brodszky et al., 2014b, Brodszky et al., 2009, Brodszky et al., 2006a, Brodszky et al., 2007, Horvath

et al., 2014, Lopez-Bastida et al., 2016b, Minier et al., 2010, Péntek et al., 2007), „Neoplasms" (n=8, 12,0%) (Boncz et al., 2010, Brodszky et al., 2017, Dasbach et al., 2010, Inotai et al., 2015, Leal et al., 2016, Vokó et al., 2012, Zemplenyi et al., 2016) and the „Diseases of the nervous system" (n=8, 10,7%) (Fejes et al., 2019, Kobelt et al., 2006, Péntek et al., 2012b, Péntek et al., 2017b, Tamás et al., 2014). (Figure 16.)

**Figure 16. The selected publications' distribution by ICD groups**



- I Certain infectious and parasitic diseases
- II Neoplasms
- III Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism
- IV Endocrine, nutritional and metabolic diseases
- V Mental and behavioural disorders
- VI Diseases of the nervous system
- XI Diseases of the digestive system
- X Diseases of the respiratory system
- XI Diseases of the digestive system
- XII Diseases of the skin and subcutaneous tissue
- XIII Diseases of the musculoskeletal system and connective tissue
- XIV Diseases of the genitourinary system
- XVII Congenital malformations, deformations and chromosomal abnormalities
- XXI. Factors influencing health status and contact with health services
- not disease specific

### 6.2.3.3. Distribution of publications: Hungarian studies and international research with the participation of Hungary

The majority of the publications (62.7%, n = 47) were in English and 37.3% (n = 28) in Hungarian. The first author of 56 publications (74.7%) was Hungarian, and another 19 publications (25.3%) were international. The distribution of the last authors was 69.3% (n = 52) Hungarian and 30.7% (n = 23) international. The majority of publications (n = 51, 68%) were studies from Hungary and 32% (n = 24) international research with the participation of Hungary.

### 6.2.3.4. Distribution of publications by Scimago ranking

Of the publications, 33 (44%) were published in Scimago Q1 journals, 13 (17.3%) in Q2 journals (Bocskai et al., 2018, Nagy et al., 2014, Brodszky et al., 2020, Rencz et al., 2017, Baji et al., 2012b, Rencz et al., 2015c, Brodszky et al., 2017, Jakubczyk et al., 2016, Dasbach et al., 2010, Brodszky et al., 2010c, Brodszky et al., 2009, Inotai et al., 2015, Tichopad et al., 2016), a further 5 articles (6.7%) (Marada et al., 2016, Péntek et al., 2008, Zemplenyi et al., 2016, Daroczi et al., 2016, Gulácsi et al.) were Q3 and 7 articles (9.3%) were ranked Q4 (Kárpáti et al., 2007, Pentek et al., 2013, Péntek et al., 2012a, Fejes et al., 2019, Harangozó et al., 2008, Bodnár et al., 2010). A total of 4 articles (5.3%) were published in unlisted Hungarian journals (Brodszky et al., 2010e, Borsos et al., 2006, József, 2006, Kósa József et al., 2008). A further 13 technology analysis reports were selected as a result of our manual search (Brodszky et al., 2006a, Brodszky et al., 2006b, Brodszky et al., 2007, Brodszky et al., 2010a, Brodszky et al., 2010b, Gulácsi, 2010, 2011a, 2011, Brodszky et al., 2011b, Brodszky et al., 2011c, Brodszky et al., 2012, Brodszky et al., 2013, Brodszky et al., 2015) which do not fall into the categories of the classification. (Figure 17.)

**Figure 17. The distribution of publications based on Scimago ranking (%)**
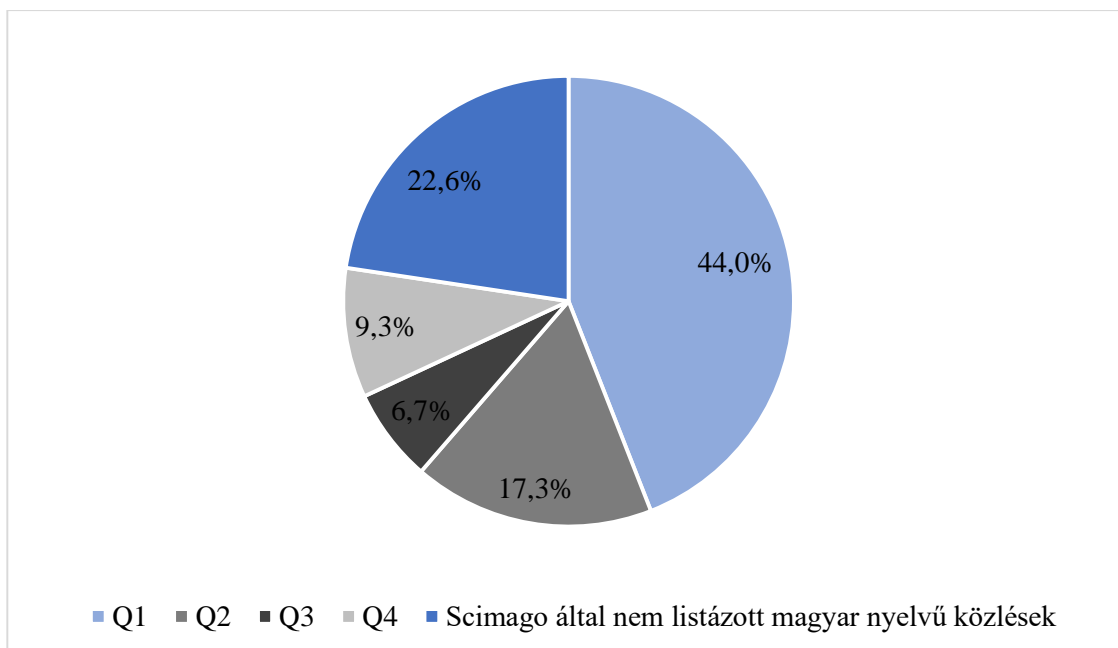


6.2.3.5. Costs in the publication

The distribution of costs in the publications by outpatient and inpatient sector is shown in Figure 18. The majority of publications (n = 36) included some cost in the inpatient and outpatient sector.

**Figure 18. Distribution of outpatient and inpatient sector cost in the publications (n)**
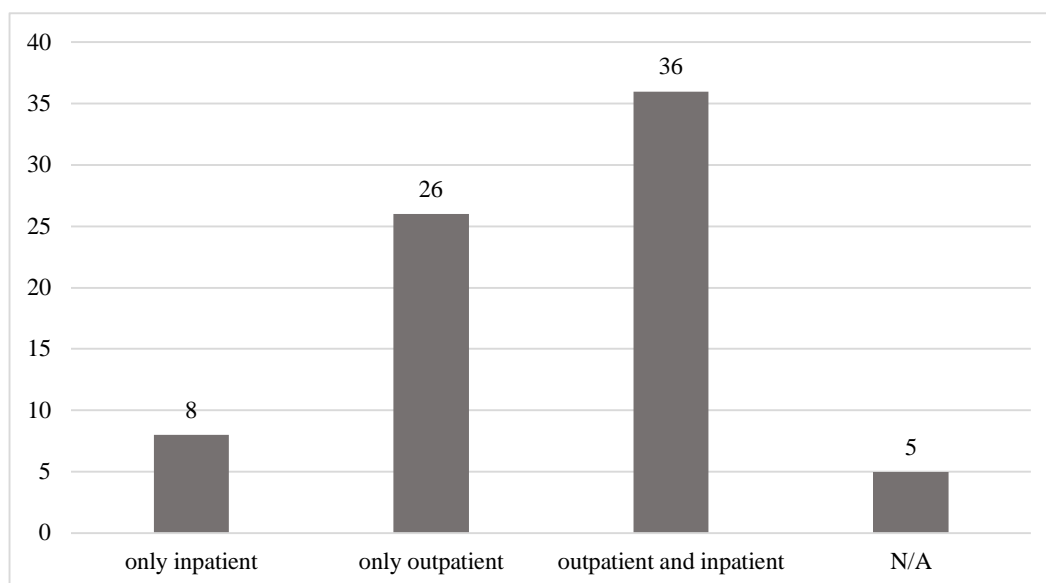


More than half of the publications (57.3%, n = 43) reported only direct costs, however, in three of the publications reporting indirect costs, the authors calculated the indirect costs after hospitalization and outpatient days, which is an estimate and cannot be considered as a methodologically appropriate indirect cost calculation (Jakubczyk et al., 2016, Meszner et al., 2017, Tichopad et al., 2013). (Figure 19.)

A total of 6 publications, reported cost data is cumulative over several years (Brodszky et al., 2017) for the whole patient population (Gulácsi et al., 2007, Horvath et al., 2014) or in the percentage of the respondents' income (informal payment) (Baji et al., 2012a), in these cases, we estimated the average costs by calculating the number of years, the number of patients / cases and the average salary in the article.

**Figure 19. Distribution of the publications according to type of cost reported (%)**
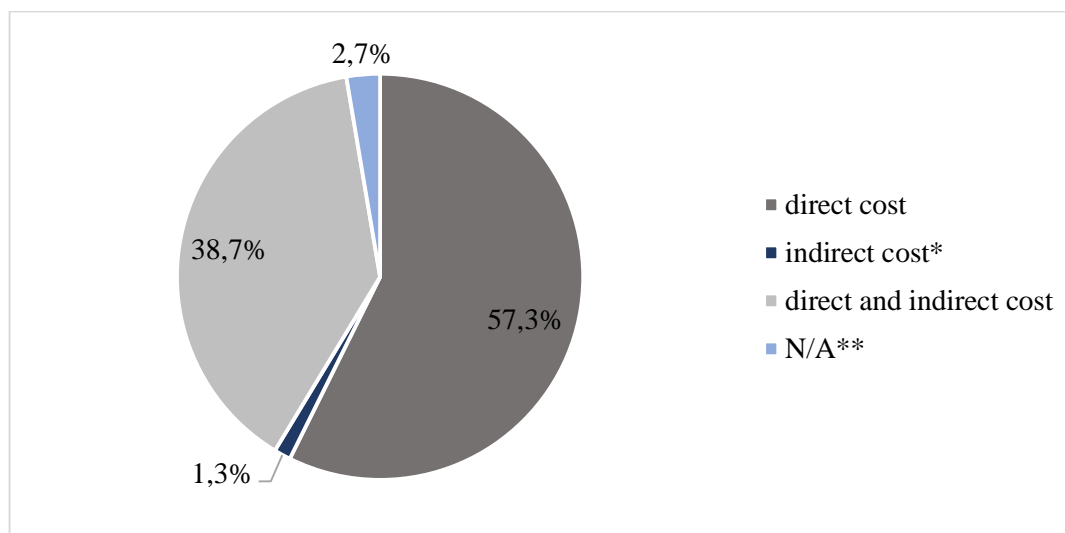


*The study only reported indirect costs (Mandel et al., 2014)**N/A: two publications, which reported informal payments (Baji et al., 2012a, Baji et al., 2012b)

6.2.3.6. Methodology of data collection (resource use) and methods of health economics analysis in selected publications

The selected publications show highly heterogeneous methods of data collection, costing, and health economics, which include:

The most common resource use data collection methodology in the selected publications was the use of a retrospective funding database and a cross-sectional study, used in a total of 57 publications (76%).

1.retrospective NHIFA database

Retrospective NHIFA database was used in 25 publications (33.3%), of which in 23 cases the authors performed an analysis of the health resources used in the given case solely on the basis of NHIFA data (Baji et al., 2018, Boncz et al., 2010, Borsos et al., 2006, Brodszky et al., 2011b, Brodszky et al., 2012, Brodszky et al., 2013, Brodszky et al., 2015, Brodszky et al., 2017, Daroczi et al., 2016, Gulácsi et al., Horvath et al., 2014, Inotai et al., 2015, Iversen et al., 2015, Jakubczyk et al., 2016, Kárpáti et al., 2007, Leal et al., 2016, Rencz et al., 2017, Tichopad et al., 2013, Vokó et al., 2012, Colombo et al., 2011, Brodszky et al., 2014b, Brodszky et al., 2006a, Brodszky et al., Marada et al., 2016,

Angelis et al., 2016a, Cavazza et al., 2016a, Cavazza et al., 2016b, Chevreul et al., 2016a, Chevreul et al., 2016b, Lopez-Bastida et al., 2016a, Lopez-Bastida et al., 2016b), and two publications used a combination of a retrospective funding database and a cross-sectional study (Brodszky et al., 2010b, Brodszky et al., 2006a). The use of health resources at different levels (primary care, outpatient and inpatient care, medicines, medical devices) was retrieved from NHIFA databases by the authors. For example, what resources were used in the treatment of prostate cancer (how many inpatients were admitted to care, what medications were used).

2. retrospective NHIFA database supplemented by the results of a cross-sectional study

We identified in two publications (2.7%) in which the use of the retrospective database was supplemented by the results of a cross-sectional study of the authors.

3.cross-sectionnal survey

A total of 34 publications (45.4%) included cross-sectional studies, of which 32 used only cross-sectional studies and two publications used a combination of retrospective review of financer's database and cross-sectional study (Gulácsi, 2010, Brodszky et al., 2006a).

In the cross-sectional studies, the authors asked in a questionnaire about the use and number of primary care, outpatient and inpatient care, medicines and medical devices (for example: how many times the patient visited their GP during the survey period) and only partially by social security. or use services and products that are not supported at all. Thereafter, if the service or product in question was subsidized by social security, the financing data of NHIFA were taken into account. In case the service and product were not subsidized by social security, the wholesale price was taken as the basis by the authors.

4. retrospective chart review

In the case of chart reviews, the authors used the documentation of elected hospitals. The resources used (for example: diagnostic tests, x-rays) were recorded and categorized into a disease group (HBCS) category, and valued with the financial value of that given group. This provides a more detailed, more accurate picture, than simply relying on the NHIFA's data, however the categorization made by the authors might not reflect the real category based on which the financing is provided.

A total of 4 (n=5.3%) publications used chart reviews (Fejes et al., 2019, Meszner et al., 2017, Tichopad et al., 2016, Vallejo-Torres et al., 2018).

5.expert opinion

6.7% (n = 5) of the selected publications referred to expert opinion as a methodology of (resource use) data collection (Coyle et al., 2018, Kovacs et al., 2014, Nagy et al., 2014, Németh et al., 2018, Trapero-Bertran et al., 2018).

6.micro-costing

During the micro-costing, the authors performed exact identification, measurement and valuation of the resources used. In our analysis, one publication reported that they used micro-coting (Zemplenyi et al., 2016).

7. quasi micro-costing

A publication using a quasi-micro-costing was also selected, in which the authors calculated the financed price of diagnostic interventions based on NEAK data, drug use data based on the patient's medical records and the gross purchase price, special tuberculocids and hotel costs were identified based on data obtained from the hospital ward (Bodnár et al., 2010).

8.published randomized clinical trials

A total of 7 publications (9.3%) were based on a published clinical trials (Brodszky et al., 2011a, Brodszky et al., 2010c, József, 2006, Kósa József et al., 2008, Scuffham et al., 2006, Brodszky et al., 2007). Cost calculation based on a randomized controlled clinical trial, in which, in the case of the group of patients described in RCT, the authors forint the processes and treatment in RCT. This is a first approximation before a medicine or other product enters the market, but neither the characteristics of the healthcare in a given country nor the impact of real circumstances are taken into account, so the results of these analyses can only be applied with great caution in practice.

9. Central Statistical Office

One of the selected publications (1.3%) used a household panel of the Central Statistical Office for data collection, in this publication the informal health expenditure of households was surveyed (Baji et al., 2012a).

The indirect cost estimates also appeared in publications in several different ways:

1.Indirect cost calculation: an estimate of the indirect costs incurred by the patient due to reduced productivity

2.Limited indirect cost calculation: in some publications, the indirect cost was calculated by the authors after hospitalization and outpatient days, which may have led to an underestimation of indirect costs.

6.2.3.7. Data sources for cost data reported in publications

The cost data used in the publications also come from a number of different sources and their identification was widely varied.

1. NHIFA

Regarding the source of cost data, a total of 80% (n = 60) of the publications included the National Health Insurance Fund Manager (NHIFA) and its predecessors as the source of cost data (primary care, outpatient and inpatient care, drug and medical device databases). These are the official funding figures from which NIHIFA calculates the actual funding amounts.

The issue of the widespread use of NIHFA data raises a number of important questions, the most important of which is the relationship between NHIFA financing and the real costs. Unfortunately, we cannot answer this question, but it is likely that the difference is significant, for the following reasons:

It is based on funding data from NIHIFA and its predecessors, in which case the problem arises that the funding data do not contain a significant health economically significant factor.

The collection of real hospital cost data needed to calculate the disease groups's values (HBCS values) has been slow for the past two decades, the system, which had been introduced in 1993m has not been modified majorly since 1999 (changing the proportions of the groups), and last comprehensive hospital cost survey last took place in 2008 (Balázs et al., 2015).

The hospital's prospective funding is not only a funding mechanism but also a health policy tool, as it is not intended to reimburse the exact costs either at the hospital level (the costs of the same interventions can vary significantly between hospitals) or at the national level.

In addition, the data is modified to an unknown extent in several cases, as service providers optimize their data provision to NHIFA, after which NHIFA checks, filters and modifies it.

In Hungary, this financing database are available, but must be handled with care, because the proportion of financing amounts to real costs is not known.

## 2. Wholesale price

Wholesale price as a source of cost data has appeared in 19 publications. The authors used the price of the corresponding service or product to estimate the cost of non-reimbursed products and services purchased by patients, as well as the cost of travel.

## 3. Central Statistical Office

In a total of 29 publications, the Central Statistical Office appears as a source of cost data, such as gross income in the case of productivity loss estimates and, in the case of measuring household health expenditure, the Central Statistical Office's household panel survey was used (Baji et al., 2012a).

## 4. Prices from other country

In two publications, the price of a biological drug was estimated from a price from another country (UK) (Baji et al., 2018, Rencz et al., 2017). It certain cases, at the time of the analysis there was no officially established NHIFA price for the medicine in question, therefore a price from other countries may have been used.

## 5. Expert opinion

A reference to expert estimation as a source of cost data has appeared in two publications (Kovacs et al., 2014, Meszner et al., 2017). In this case, the price of the given item was not available to the authors, hence experts' opinion was used.

## 6. Not accurately identifiable data

In 9.3% of publications (n = 7), the source of cost data was marked as multiple data sources, and could not be identified accurately (Bocskai et al., 2018, Coyle et al., 2018, Németh et al., 2018, Trapero-Bertran et al., 2018, Harangozó et al., 2008, Jakubczyk et al., 2016, Vallejo-Torres et al., 2018). These were mostly international research with the participation of Hungary.

## 7. OECD average wage

In one publication, the authors used the OECD average wage to estimate indirect costs (Meszner et al., 2017).

8. Estimated based on patients' answers

In one of the selected publications, the amount of informal payment paid by the patients was estimated based on the responses of the patients included in the study (Baji et al., 2012b).

6.2.3.8. Perspective

The costing perspective has been indicated for most of the publication. However, in 16 (20%) publications, the perspective of costing was not indicated (Brodszky et al., 2011a, Baji et al., 2012a, Baji et al., 2012b, Daroczi et al., 2016, Fejes et al., 2019, Harangozó et al., 2008, Inotai et al., 2015, Iversen et al., 2015, József, 2006, Leal et al., 2016, Meszner et al., 2017, Péntek et al., 2007, Péntek et al., 2017c, Péntek et al., 2008, Tichopad et al., 2013), their perspectives were identified during the analysis of the publications by categorizing the reported data: in nine cases it was societal (Harangozó et al., 2008, Inotai et al., 2015, Jakubczyk et al., 2016, Leal et al., 2016, Meszner et al., 2017, Péntek et al., 2007, Péntek et al., 2008, Tichopad et al., 2013, Baji et al., 2012a), and in seven cases we could assume a payer perspective (Brodszky et al., 2011b, Bocskai et al., 2018, Daroczi et al., 2016, Fejes et al., 2019, Iversen et al., 2015, Kósa József et al., 2008, Péntek et al., 2017c).

Social perspective was used in a total of 38 publications (50.1%) of which 29 publications indicated the social perspective (38.7%) and in nine cases (12%), the social perspective was identified during the analysis of the data (Harangozó et al., 2008, Inotai et al., 2015, Jakubczyk et al., 2016, Leal et al., 2016, Meszner et al., 2017, Péntek et al., 2007, Péntek et al., 2008, Tichopad et al., 2013, Baji et al., 2012a).

Payer perspective was used by 37 publications (49.3%). Out of which 22 reported the perspective clearly (29,3%). In addition 2 publications indicated (2.7%) the „healthcare system" (Coyle et al., 2018, Marada et al., 2016), 2 publications (2.7%) the „social insurance" (Horvath et al., 2014, Kárpáti et al., 2007), 3 publications (4%) the provider (Bodnár et al., 2010, Vallejo-Torres et al., 2018, Zemplenyi et al., 2016) and one publication (1.3%) indicated the government (Scuffham et al., 2006) as the perspective used. These were considered a payer perspective. In seven cases (9.3%) the perspective of the cost calculation was not indicated, and the payer perspective was identified during

the analysis of the data. (2011, Bocskai et al., 2018, Daroczi et al., 2016, Fejes et al., 2019, Iversen et al., 2015, Kósa József et al., 2008, Péntek et al., 2017b).

# 7.    DISCUSSION

## 7.1.  Health-related quality of life
### 7.1.1.  A Comparison of European Polish, Slovenian and British EQ-5D-3L value sets using a Hungarian sample of 18 chronic diseases

We analysed the index values calculated with the four different sets of EQ-5D-3L values and the potential effects of this deviation in a total of 18 different diagnoses. Our analysis included several different diseases. Using cross-sectional samples from Hungarian patient populations (Rencz et al., 2016, Brodszky et al., 2009, Brodszky et al., 2010d, Érsek et al., 2010, Simoens et al., 2012, Pentek et al., 2013, Hever et al., 2015, Rencz et al., 2015a, Balogh et al., 2013, Tamás et al., 2014, Rencz et al., 2014, Péntek et al., 2007, Péntek et al., 2012b, Minier et al., 2010, Péntek et al., 2012c, Péntek et al., 2012a, Balogh et al., 2014, Pulay et al., 2016). We analysed value sets which are often used or potentially used in health economics analyses in the Central and Eastern European region (Rencz et al., 2016). Using patient-level data, we compared the utility values calculated with the four different value sets

Previous studies has compared other TTO and VAS-based sets of values in several countries using, for example, population sampling, modelling, or analysis of a specific patient population (Mozzi et al., 2016, Endarti et al., 2018, Bernert et al., 2009) (Clemens et al., 2014) (Olsen et al., 2018). Furthermore, several other previous studies have compared value sets in each EQ-5D-3L profile (Kiadaliri, 2016, Golicki et al., 2010, Brooks et al., 2003). In our current research, we compared value sets that are based on two different methods (TTO and VAS) in several patient populations with different diagnoses.

We found significant differences in our analysis by diagnosis, age group, and disease severity. The mean EQ-5D-3L index value difference was 0.265 in the PD diagnosis and 0.187 in the 55-year-old group. Pairwise comparisons of disease burden (DB) yielded inconsistent results in comparing value sets based on different methodologies (TTO vs.

VAS). However, when comparing value sets based on the same methodology, we obtained consistent results.

Our results confirm the hypothesis in previous research that methodological differences can be observed in the EQ-5D-3L value sets. (Olsen et al., 2018, Bernert et al., 2009). The discrepancy between the EQ-5D-3L value sets can lead to a significant discrepancy in utility values, thereby they may influence the assessment of health gains. Looking at an example, if a patient's health status had moved from '22222' (a moderate problem in all dimensions) to '11111' (perfect health) (e.g. due to the effects of a new therapy), the QALY gain would be 0.685 with the Slovenian, and only 0.284 with Polish value set Moving from the worst possible health state ('33333') to the '22222' state would mean a gain of 1,239 QALY with the Polish value set, but only 0.555 calculated with the European value set.

Because of the significant differences observed between the value sets, the choice of value set can greatly affect the utility of a condition and thus influence the priorities set in health policy and funding decisions.

These factors may be particularly important in the Central and Eastern European region, where in many cases local data are not available and health economics analysis often have to rely on external data sources (Gulácsi et al., 2016). The need to develop country-specific value sets is increasing, as local value sets could better reflect the preferences of a given population (EuroQol, 2019).

However, our research had certain limitations. The patients in our research do not always represent the entire patient population with a given disease. Further research involving several diseases would contribute to a better and deeper understanding of the differences in EQ-5D-3L index values established with the different value sets.

In summary, it can be concluded that comparing different value sets on a sample of patients with chronic diseases, the importance of value set choice can be discovered and influence health economics analysis and preparation of health policy decisions.

Public policy significance

The choice of values is an important factor in the process of health economics analysis and health policy decision making.

Information on the utility of health conditions is essential for learning about individual and social benefits, and for planning a 'fair' resource allocation, as this will ensure that everyone receives care that meets their health needs in a transparent manner. The results of the research show that country-specific differences in quality of life cannot be ignored. In order to allocate health care resources in Hungary (similarly to the practice of developed countries) in accordance with the preferences of the Hungarian population, it is necessary to use an appropriate value set. This would ensure that healthcare meets the real needs of the population and that resource allocation decisions become more appropriate and transparent, and that information asymmetry could be controlled.

### 7.1.2. A detailed analysis of 'not relevant' responses on the DLQI in psoriasis: potential biases in treatment decisions

In the present study, we analysed the incidence of NRR responses in the DLQI questionnaire among patients with psoriasis. Our results showed that the total DLQI score, PASI score, and several socio-demographic factors influenced how many NRR responses a patient indicated.

More than one third (38.8%) of the patients reported at least one NRR response, and more patients with DLQI scores between 6 and 20 were candidates who reported an NRR response than those who did not. This suggests that certain areas appearing in DLQI are not significant in a significant proportion of psoriasis patients. Furthermore, since NRR responses receive a score of 0, a higher incidence of NRR responses would lead to a lower overall DLQI score. However, the results of our research show that the higher the total DLQI score, the more NRR responses patients mark. The inverse relationship between the high frequency of NRR responses and the total DLQI score and the number of NRR

responses suggests the existence of a validity problem. By omitting the questions with the NRR response and switching the resulting score to a scale of 0–30, the mean total DLQI score of the 166 patients with the NRR response increased from 7.23 to 8.94 (p <0.001). This increase was even more significant in the group over 65 years of age (n = 46), where the average would change from 7.41 points to 10.15 points (p <0.001).

We observed that groups with certain socio-demographic characteristics were more likely to choose the NRR response. In our sample, these groups were women, the elderly, part-time workers, and those with lower levels of education.

Similarly, to previous studies, the NRR response was most common in sports, sexual difficulties, and work-related questions (Hahn et al., 2001, Mork et al., 2002, Twiss et al., 2012, Ferraz et al., 2006, Khoudri et al., 2013, Mazzotti et al., 2005, Mayrshofer et al., 2005). These questions are less relevant for older psoriasis patients than for younger ones. However, psoriasis is a lifelong, chronic disease, and, it is important that the outcome measures that are should be applicable to all ages.

Our research had several limitations. Despite the large sample size, there were less than 10 NRR responses for some questions and few patients reported more than 2 NRR responses. Furthermore, we do not have information on whether the patients in our sample were able to distinguish between NRR and "not at all" responses, which may be a misinterpretation of the previously highlighted problem with the questionnaire (Pentek et al., 2017).

Two other studies also focused on the evolution of NRR responses in the DLQI questionnaire (Bashyam et al., 2019, Langenbruch et al., 2019). Langenbruch et al. analysed DLQI responses on a sample of 1240 patients with psoriasis. They found that 48.7% of patients did not label any NRR response. Bashyam et al. also highlighted the problem of choosing "not relevant" answers and stated that respondents may not always be able to distinguish that their illness prevents them from engaging in an activity or that they have no interest in doing the activity at all (Bashyam et al., 2019, Langenbruch et al., 2019).

Public policy significance

Disease-specific questionnaires are in many cases used to set up a therapeutic indication and to evaluate the benefits of a particular therapy. That is, the results of these questionnaires may influence how many and in what health condition (need) an individual will receive a particular therapy. In this research, we have seen that a patient's access to therapy, in addition to his or her state of health, can be influenced by other socioeconomic, gender, age, and geographic characteristics of the individual. We do not consider this to be acceptable in the context of publicly funded healthcare, as it runs counter to the public policy objective of providing healthcare to the patient based on his or her needs.

Access (which patient in which health state has access to a therapy) has an impact on cost-effectiveness and this data is extremely important when examining the budget impact of a given therapy. Cost-effectiveness and budget impact are influencing the decisions (on a national level whether) a given patient has access to a given medicine within the framework of publicly funded healthcare.

### 7.1.3. The health state and productivity of the Hungarian general population

The aim of our research was to assess the health status and productivity of the Hungarian population using standard methods. With an aging society and an increasingly efficient health care system, funding, the planning and provision of health services, and the sustainable employment of patients with chronic illnesses have become key priorities. Cost-effectiveness analysis based on local (country-specific) data are needed for decision-making and evaluation of new technologies. In order to create sustainable employment and support the health policy decision-making process, local data, (regarding the health status of a population, labour productivity and knowledge on the relationship between the two factors) can be important information. We conducted a cross-sectional questionnaire survey among the Hungarian population, involving a representative sample. We used standard measures in our research. A total of 2,023 respondents participated in our questionnaire survey.

The mean of the EQ-5D-5L index value was 0.92 (SD = 0.15) and the mean of the EQ-VAS was 81.6 (SD = 17.4) among the participants. In WPAI, the average productivity

loss in other activities was 9.5% (SD = 21.0%), the average value of total productivity loss at work was 7.7% (SD = 20.9%), in the case of absenteeism and presenteeism mean values were 3.6% (16.4%) and 4.4% (14.2%), respectively.

Wrona et al. analysed the decline in productivity due to health status (as measured by the WPAI-GH questionnaire) for the Polish population and their results were similar to those in other European countries. Examining groups with different incomes, it was found that total productivity loss at work was higher for higher-income households (Wrona et al., 2010). In the present research, we found a significant relationship between the net monthly income of the household and the productivity loss in other activities. (r=-0,277, p=0,000).

Mandel et al. also analysed the productivity loss in Hungary among people with inflammatory bowel disease and found that presenteeism and absenteeism were frequent (Mandel et al., 2014). In another study, also conducted in Hungary, Péntek et al. also used the EQ-5D and WPAI questionnaires to measure health-related quality of life and productivity among women with hyperactive bladder syndrome. Based on the results of Péntek et al. presenteeism was extremely significant among the patients studied (Péntek et al., 2012a).

Public policy significance

Therapies are extremely important not only for the elimination of clinical symptoms, but also for the restoration of an individual's quality of life, social abilities, and ability to work. However, routinely collected data on these factors are not available, so in order to know the full benefits of therapies, it is necessary to examine them with health economics analyses. For optimal resource allocation and decision making, it is extremely important to fully understand the benefits of therapies.

### 7.1.4. Characteristics and determinants of informal care in chronic diseases in Hungary: A comparative analysis

In our research, we examined informal care among Hungarian patients by analysing patient-level data from our previous surveys of 14 chronic diseases.

A quarter (27%) of the patients received help from an unpaid helper, with an average of 7.5 hours of informal care per week for the entire patient sample and a significant difference between diagnoses. In dementia, four inflammatory immunological diseases (RA, SSc, AP, and SM) and Parkinson's disease, the highest rates of patients received informal care. (Figure 10.) The highest number of hours was also found in these diseases. (Figure 11.) The dependence of people with dementia on informal care is significant in Hungary as well, and our results are in line with international data (Costa et al., 2013). The difference in the results in dementia compared to other diagnoses may also be due to the fact that the time of informal care was measured with a dementia-specific questionnaire (the so-called RUD questionnaire), which recorded in detail the time spent on various activities and patient care and the number of care per week. Another difference is that in dementia, the relatives caring for the patient answered the questions, not the patients themselves. Carers may judge in differently what activities are included in informal care and how much time the carer (or carers) has spent on it.

The methodology of informal care surveys is not uniform in the literature, to increase comparability, a disease-independent standard questionnaires (such as the iMTA Valuation of Informal Care Questionnaire - iVICQ) are increasingly used, and their use in Hungarian surveys should be considered (Hoefman et al., 2011). In Parkinson's disease, informal care has been shown to be significant in other countries, averaging 10 hours per week in the Czech Republic and Russia, but much higher hours have also been reported. (Bovolenta et al., 2017, Rodríguez-Blázquez et al., 2015). The inflammatory immunological diseases (RA, AP, SM, SSc) in our study typically had high disease activity, which partly explains the high informal care time (Brodszky et al., 2009, Minier et al., 2010, Péntek et al., 2012b, Péntek et al., 2007). It would be worthwhile to examine in future research how the costly but effective biological therapies (especially in RA and AP) has changed informal care use and its costs, for which, there is no routinely collected data available (Gulácsi et al., 2016).

The average age and disease duration of those receiving informal care was only slightly higher than that of those not receiving informal care. More than twice as many women received informal care as men, while the proportion of women in the overall sample was only slightly higher. (Table 8.) Among the possible causes (e.g., difference in disease severity between men and women in the samples), it should also be considered that the surveys were based on patients' self-reports except for dementia. Depending on what

activities someone performed before the illness (cooking, washing or cleaning), they may judge differently what is considered informal care (Hoefman et al., 2013). Although our research did not examine this, it is possible that a higher proportion of women became unable to carry out their previously normal household tasks due to the illness and therefore more of them considered that they needed help from others.

We consider it important to emphasize that in our research we examined actual informal care and not the need for informal care. There may have been more patients in need of informal care, who did not receive any. Among those who did not receive informal care, there were more patients living alone, and it is possible that this was the reason some of them did not receive informal care. (Table 9.)

Patients receiving informal care had significantly worse general health (EQ-5D-3L) than those who did not. (Table 9.) Among the dimensions of the EQ-5D-3L questionnaire, the largest differences were found in the Usual activities and Self-care dimensions between the two subgroups, with many more informal care recipients reporting some or severe problems in these areas. (Figure 12.) Our regression analysis confirmed our hypothesis: we found a significant relationship between informal care time and EQ-5D results. (Table 10.) The gender of the patient also proved to be a significant determinant, and of the 14 diseases examined, the association was significant in osteoporosis and Parkinson's disease. Applying an 8-hour care time limit per day, we obtained similar results. However, the variables included in the analysis only partially explained the informal care time. (Table 10.) Larger sample studies are suggested and exploring additional influencing factors (e.g., more detailed socio-demographic characteristics, caregiver health status and quality of life related, carer-caregiver relationship) are interesting areas for future research.

Although informal care hours and patient's health status measured with the EQ-5D questionnaire have been reported in a number of studies in the international literature, there are only a few publications analysing the relationship between the two. Brouwer and colleagues examined the relationship between patient quality of life, caregiver's ability to work and informal care in the Netherlands in RA (Brouwer et al., 2004). In Sweden similar studies were conducted in dementia (Neubauer et al., 2008, Wimo et al., 2012). The studies with the highest number of cases was conducted in Germany by Rowen et al. (Rowen et al., 2016). In their analysis based on a questionnaire study of 44,500

participants, they found that a 0.1-point improvement in health measured by the EQ-5D index score could reduce informal care time by less than 1 or even more than 2 days over a six-week period, depending on the modelling method. Thus, the time gained by caregivers by improving the patient's condition is significant, hence it is worthwhile to conduct further research in this field and at the same time examine the changes in the quality of life of the caregivers.

The limitations of our research should also be mentioned. Only those local studies where patient-level data were available were included in our analysis, although to the best of our knowledge, other Hungarian research groups did not report any surveys containing both informal care and EQ-5D-3L data. Clinical areas that may be important for informal care have not been studied due to lack of data — such as oncology, end-of-life conditions, diabetes in old age, hearing loss, COPD —, it is recommended to conduct surveys in these diseases in the future. Surveys with the five-response, more sensitive version of the EQ-5D questionnaire (EQ-5D-5L) may provide a more accurate picture of the relationship between informal care and patients' health status (Angelis et al., 2016b, Lopez-Bastida et al., 2016a, Lopez-Bastida et al., 2016b, Kuhlmann et al., 2016, Cavazza et al., 2016b, Péntek et al., 2014, Péntek et al., 2016a, Rencz et al., 2014, Cavazza et al., 2016a). It would be worthwhile to further examine patients' expectations, the relationship between disease stages and informal care in larger samples, including standard disease-specific measures (Herédi et al., 2014, Rencz et al., 2015a). In our research, we did not examine the access and use of formal care (health and social care, residential homes, day care centres), which may also influence the informal care needs and burden.

We believe that despite these limitations, our research provides a valuable summary and analysis of informal care and its determinants in a wide range of chronic diseases in Hungary. Based on our results, the burden on the family, especially for diseases leading to disability, is very significant. Changes in the life of a patient's family during treatment — including the quality of life of carers and the costs of informal care — are worthwhile and necessary to assess in order to get a complete picture of the disease burden and the results achieved with successful treatment.

Public policy significance

Our research provides data for further health economics analysis, as well as highlights the importance of research on informal care, methodological challenges, and significant areas

of research that have not yet been explored. From a public policy perspective, the disease burden of each health problem needs to be examined from a societal perspective. We need to identify and measure all the factors that contribute to the social burden and may be relevant. Typically, informal care may be overlooked, but cause a significant social burden.

We hope that our analysis will give momentum to research on informal care in Hungary, thus making patient care more efficient and successful.

## 7.2.  Costing

### 7.2.1.  Cost of informal care in chronic diseases in Hungary: A comparative analysis

The results of our study clearly confirmed that the cost of informal care is very high in Hungary, similarly to the international data. The research used in the present study included patients who had received outpatient care or hospitalization due to their illness, and the patient samples represented a group of these patients.

However, to calculate the exact amount of informal care cost, we would need information on what extent our study results can be generalized to the entire population of those with the diseases we studied. This information is not available in the databases of routinely collected data (NHIFA and other public health databases), and we would need this to calculate the amounts reliably (KSH, 2009, OECD, 2017). There are various surveys reporting data on how many people provide or receive informal care in the elderly population, in Hungary. However, these do not contain data related to specific diagnoses or health conditions, so they are not suitable for estimating the disease burden caused by different diseases in health economics analysis.

Measuring the cost of informal care also appears in international studies. Rheumatoid arthritis also appeared in a systematic literature review by Krol et al. The authors found results on a wide range of costs for informal care for rheumatoid arthritis patients (569 EUR to 181,620 EUR) (Krol et al., 2015).

Knowledge of these amounts is necessary for health policy to be able to assess the real social cost and importance of diseases. Without knowledge of the costs of informal care, it is not possible to make informed health policy and funding decisions. Surveys clearly show the population and patients' need for informal care. Increasing life expectancy and caring for an increasing number of chronic patients are predictably in the future. However, the number of people living in the same household is not high and is expected to decrease, which is why the number of informal providers is expected to decrease.

In the absence of informal care, the care must be provided by the public or private providers, i.e., formal health care, which anticipates significant additional capacity, labour, and cost demands. It should be mentioned that there is still a significant shortage of specialists in the healthcare and social sectors, and it does not seem possible to involve a larger number of specialists.

In the future, it would be necessary to observe the need for informal care in Hungary in order for the need for care and financing to be known and plan for care needs and financing, either for the state or for insurers. Furthermore, it would be useful to also analyse the unfulfilled needs, and thus to identify the groups, including the most vulnerable patients, who do not receive adequate care.

Among the limitations of our analysis, it should be mentioned that the national estimate was made on the assumption that the patients included in the research are well representative of all patients in Hungary suffering from the studied disease. In the studies, we did not take into account that a patient may have multiple chronic illnesses, so we could overestimate the cost. The extent of the bias is invaluable without further research. Another possible bias is that we only measured the informal care received, we have no information on patients who needed informal care, but did not receive any. Because of this, we may have underestimated the actual costs. As a further limitation, it is important to mention that the number of hours of informal care was derived from studies conducted in different years, and the was taken into account when calculating 2017 costs. However, over time, the treatment of many diseases may have changed significantly, and the introduction of new effective therapies may have modified the number of hours of informal care in some patient subgroups (e.g., patients with rheumatoid arthritis now treated with biologics).

Public policy significance

Without full knowledge the specific costs, no proper public policy decision can be made. Based on our results, we believe that the estimated costs are high and the cost of informal care is significant in Hungary. Thus it is necessary to learn about the real social burden, make appropriate health policy decisions and develop sustainable financing.

### 7.2.2. Cost-of-illness studies in nine Central and Eastern European countries

As a result of our literature search, we identified 58 studies (containing 83 country-specific results) that reported disease cost (COI) data for Austria, Bulgaria, the Czech Republic, Croatia, Hungary, Poland, Romania, Slovakia, Slovenia. the most commonly discussed clinical area was endocrine, nutritional, and metabolic diseases. The reporting of costs in euros was dominant, which may suggest researchers in the region find it important to make their results available for international comparison.

The issue of transferability arises in many cases, however, the methodological heterogeneity discovered in the 58 studies examined may make this significantly more difficult in the CEE region. To assess the quality of the publications, we examined the description of the methodology used. We consider it important to point out that the data sources of resource use and the year of cost calculation were reported in almost all publications (98% and 95%, respectively), many other extremely important indicators were reported in far fewer cases.

The perspective used was indicated in 78% of the publications, the approach used to measure indirect costs was 77%, the methodology of cost calculation was 64%, at least one unit cost was 42%, and the method of evaluating informal care was 31%.

A review of recent analyses in Austria found that the year of prospecting and costing was not reported in 60% and 25% of the research. The differences can be explained by the selection of "gray literatures". Mayer et al. discussed 93 economic analyses, 14 of which were disease cost surveys. Furthermore, of the 93 studies, 23 were non-indexed and 12 were non-peer-reviewed publications (Mayer et al., 2017).

Different studies discussing a disease have shown large differences across countries, but comparability varies from study to study.

The methodologies used were very different in many cases, and the differences in the samples included in the research (sample size, average age of the participants in the sample, diagnosis, available therapies) should also be taken into account in many cases. Differences in unit costs can also contribute greatly to differences in results (Mayer et al., 2017).

In bladder cancer research, for example, the cost of a hospital day was 7 times as high in Austria (495 EUR) as in Romania (67 EUR) (Leal et al., 2016). Methodological differences such as incidence vs. the prevalence-based research methodology also hinders cost comparisons. Just as the incidence-based article on prostate cancer by Brodszky et al. is not comparable to the prevalence-based article by Inotai et al., which is also discussing prostate cancer, despite the fact that both are from Hungary (Brodszky et al., 2017, Inotai et al., 2015). Due to the differences in health systems, we can also observe very different costs results in different countries.

During the past two decades, several publications were focusing on the question of transferability (Nixon et al., 2009, de Pouvourville et al., 2005, Drummond et al., 2003, Barbieri et al., 2010, Mandrik et al., 2015, Gulácsi et al., 2014a). Currently, health Economics and HTA Directives in the Central and Eastern European region contain either very limited or no directive on transferability and adaptations. Therefore, the development of a directive on the conduct of cost of illness studies would be extremely valuable for the countries of the region (Gulácsi et al., 2014a).

Our present research has several limitations. We conducted a systematic literature search to identify relevant publications, however, the possibility arises that relevant literature has not been identified and selected. Some disease cost results may not appear in our review because we have excluded conference abstracts and reports from our search. Manual searches of non-indexed journals were performed in only three countries. An additional limitation is that we did not use a comprehensive checklist, as to our knowledge this was not available for cost of illness studies in English or Hungarian. This may skew our conclusions about the quality of the studies, but we believe that the study characteristics presented may provide a good comprehensive description of the selected publications.

Public policy significance

Due to the differences of health systems, we can also observe very different cost results in the different countries. In order to make financing decisions, it is necessary to carry out analysis in accordance with the specifics of the given country. Limited transferability (cost data cannot be transferred from one country to another) and legal requirements also point to the need to use local data.

### 7.2.3. Hungarian cost library

We conducted a literature review of health economics publications in Hungary and identified the unit costs reported. The need to develop a cost library (healthcare cost catalogue) in Hungary has already came up in many cases since the accession to the EU in 2004, as the use of local data is extremely importance in all health economics analyses.

A professional description of the creation of the 'cost-library' in Austria was published by Mayer et al. They identified cost elements to be included in the "cost-library" during the analysis of published sources. In their systematic literature search (covering the period 2004-2015), Mayer et al. selected a total of 93 publications in German and English, 87% of which were journal articles; according to the clinical area, the diseases of the ICD main group "Diseases of the circulatory system" appeared most often (n = 15). Of the selected articles, 14 were cost of illness analysis. The difficulties (and importance) of the work are shown by the fact that Mayer and colleagues highlight that 60% of the articles did not clearly describe the research perspective, more than a quarter did not indicate all sources, and nearly 40% of the publications did not communicate all relevant unit costs (Mayer et al., 2017).

We conducted a literature search in order to identify and collect unit costs for Hungary. Our search currently only covered publications published in Hungary. In the future, it may be advisable to expand our data with similar data from Central and Eastern European countries. In this case, our assumption is that the health cost data of countries with similar social and economic conditions are closer to each other and can be utilized better than those of countries further apart in this respect.

Public policy significance

One of the most significant elements of healthcare decision-making is the optimization of resource allocation. However, this requires knowledge of the cost and societal burden of each disease and the costs of the treatments available to treat them.

# 8.   NEW RESULTS

## 8.1. Health-related quality of life

### 8.1.1.  A Comparison of European Polish, Slovenian and British EQ-5D-3L value sets using a Hungarian sample of 18 chronic diseases

We found methodology based differences between the value sets. The choice of value set may affect utility of health states significantly and could affect health policy decision making.

### 8.1.2.  A detailed analysis of 'not relevant' responses on the DLQI in psoriasis: potential biases in treatment decisions

We were the first to report the detailed analysis of the 'not relevant' responses on the DLQI questionnaire. We found that the incidence of 'not relevant' responses is common. They are more likely to occur among older, less educated, and female patients, so these patients may be at a disadvantage due to the specifics of DLQI scoring.

### 8.1.3.  The health state and productivity of the Hungarian general population

We assessed the Hungarian general populations ICECAP-A and ICECAP-O scores alongside the use of the EQ-5D-5L and WPAI questionnaires.

### 8.1.4. Characteristics and determinants of informal care in chronic diseases in Hungary: A comparative analysis

For the first time in Hungary and in the region, we assessed and published results on the use of informal care and its relation to health-related quality of life in 14 chronic diseases, and provided data for further health economics analysis.

## 8.2. Costing

### 8.2.1. Cost of informal care in chronic diseases in Hungary: A comparative analysis

We analysed the informal care cost in Hungary and in the region on a large sample and found that these are significant and comparable to that of other countries.

### 8.2.2. Cost-of-illness studies in nine Central and Eastern European countries

We analysed the relevant publications and compared the cost of illness results across several countries in the Central and Eastern European region. The results of our analysis show that the generally accepted opinion that the disease burden results of the countries of the region are transferrable between countries is not realistic. This is due to a high degree of methodological heterogeneity and a lack of standards.

### 8.2.3. Hungarian cost library

Due to the need for utilizing local data, we created the fourth country specific cost library in Europe, by identifying the relevant publication.

# 9. SUMMARY AND CONCLUSIONS

In the dissertation I wanted to examine the role of disease burden and quality of life in in health care decision making, which is a particularly important issue, as the disease burden and costs of chronic diseases are significant and growing not only at the individual but also on a societal level.

The economics of chronic diseases is a particularly important issue from the health policy's' point of view, as knowledge of costs and outcomes is needed to create sustainable financing and to achieve optimal resource allocation. Assessing the burden of disease also provides essential information for health policy decision makers when analysing the cost-effectiveness of therapies.

The research areas discussed in the dissertation and the data included in these research are therefore absolutely necessary for the preparation of financing decisions in order to optimally organize the allocation of resources.

In many cases, we do not have enough information about some of the burdens such as the cost of informal care provided by relatives or the cost of labour productivity loss. It is important to point out that these data cannot be found in routinely collected databases, so the total social burden of their costs and thus of the diseases is not known.

Another important factor in relation to illness is quality of life. Data on quality of life and the social dimension of quality of life are also not collected in routinely created databases, which raises the problem of not being able to fully measure the outcome of therapies, as therapies often not only aiming to eliminate clinical symptoms but to improve quality of life and rebuild skills. Data on all this can only be learned from this health economics research.

In the dissertation we discussed the research covering the field of quality of life measurement and cost calculation: During the examination of the quality of life we examined the general EQ-5D and a disease-specific questionnaire, and the quality of life, social skills and productivity loss in the Hungarian general population. In the dissertation,

we paid special attention to the analysation of the use and costs of informal care, and we found that these are extremely significant in Hungary as well.

In order to examine the cost of diseases, the dissertation presents an overview of cost of illness studies in the region, i.e. in nine Central and Eastern European countries. Based on the results, we can conclude that the usability and transferability of the cost data published in the region is strongly limited, as we encountered great methodological heterogeneity in the publications.

The Hungarian cost library also plays a significant role in learning about the costs of illness and the financing of health care. In Hungary, the almost exclusive source of cost data is currently the databases of the National Health Insurance Fund (which do not contain a lot of data that are essential for health economic analysis (e.g. direct non-health costs, indirect costs, disease severity outcome). For this reason, there is a great need for a catalogue of healthcare costs in Hungary, which includes a wider range of costs. In the dissertation, the process of developing the Hungarian health care online cost catalogue was published: we conducted a literature search in order to identify the relevant publications. Using the 75 selected publication, we developed the Hungarian cost library's structure and the analysed characteristics and quality of the publications.

The use of health economics results in health policy decision-making is significantly hampered by the fact that the methodology used in the publications is extremely heterogeneous, not always fully described, the source of the data is often not clearly identifiable and the real costs do not necessarily coincide with funding amounts.

# 10. ANSWERS TO THE HYPOTHESES

## 10.1. Health-related quality of life

*A Comparison of European Polish, Slovenian and British EQ-5D-3L value sets using a Hungarian sample of 18 chronic diseases*

Hypothesis 1.

We assume that the European, Polish, Slovenian and UK EQ-5D-3L value sets do not differ significantly

*Our results suggest that the value sets show significant differences, we reject Hypothesis 1.*

1.1. We assume that applying different value sets in the 18 chronic diseases that we examined, the health policy and funding decisions based on the results do not differ significantly in different countries.

*Our results suggest that the use of different value sets would cause differences in health policy decision making, hence we reject Hypothesis 1.1.*

*A detailed analysis of 'not relevant' responses on the DLQI in psoriasis: potential biases in treatment decisions*

Hypothesis 2.

We assume that the 'not relevant' answers of the DLQI questionnaire differ in the different demographic groups.

*Our research results show that there may be significant differences in not relevant responses between groups with different demographic and socioeconomic characteristics, accordingly, we accept Hypothesis 2.*

2.1. We assume that the effect of the differences on medical decision-making and resource allocation can be observed.

*Our results suggest that the effect of the differences on medical decision-making and resource allocation can be observed and significant, hence we accept Hypothesis 2.1.*

*The health state and productivity of the Hungarian general population*

Hypothesis 3.

We assume that the health status and work productivity of the Hungarian general population can be adequately measured by the standard questionnaires we used.

*The health status and work productivity of the Hungarian general population can be adequately measured by the standard questionnaires we used, hence we accept Hypothesis 3.*

*Characteristics and determinants of informal care in chronic diseases in Hungary: A comparative analysis*

Hypothesis 4.

We assume that the characteristics and determinants of informal care in Hungary are similar to what can be observed in other countries.

*Our results suggest that the characteristics and determinants of informal care in Hungary are similar to the results in other countries, hence we accept Hypothesis 4.*

## 10.2. Costing

*Cost of informal care in chronic diseases in Hungary: A comparative analysis*

Hypothesis 5.

We assume that the social burden and cost of informal care is very significant in Hungary as well, in accordance with international experience.

*Our research results show that the social burden and cost of informal care is significant in Hungary and is in line with international experience. In Hungary, this burden is lower in absolute terms than in the higher GDP/capita countries, but in similar proportions, accordingly we accept Hypothesis 5.*

*Cost-of-illness studies in nine Central and Eastern European countries*

Hypothesis 6.

We assume that the costs of illness in Hungary are similar to those in other Central and Eastern European countries.

*Our research results show that the costs of illness in Hungary are similar to other Central and Eastern European countries, so we accept Hypothesis 6.*

6.1. We assume that in Hungary the cost data published in other Central Eastern European country can be utilized and transferred better than the cost data originated in countries with high national income.

*The results of our research show that the usability and transferability of cost data published in Central Eastern European countries is strongly limited, we assume that the results of other countries (e.g. UK) can be better transferred, accordingly we reject Hypothesis 6.1.*

*Hungarian cost library*

Hypothesis 7.

We assume that a Hungarian cost library can be created as sufficient local data is available.

*Our results suggest that sufficient local data is available in Hungary to create a local cost library, hence, we accept hypothesis 7.*

7.1. We assume that the Hungarian cost library can contribute to the development of appropriate and sustainable health care financing decisions.

*The data needs of the current health care reforms show that such data are needed more than ever before, therefor we accept the hypothesis 7.1.*

*7.2. We assume that the Hungarian unit costs and cost are significantly different than what can be observed in high-income countries*

*Our research results show that Hungarian unit costs and costs differ significantly from those of high-income countries, we accept the hypothesis 7.2.*

# 11. OWN PUBLICATIONS RELATED TO THE THESIS

Zrubka Zs, **Beretzky Zs,** Hermann Z, Brodszky V, Gulácsi, L, Rencz, F, Baji P, Golicki D, Prevolnik-Rupel V, Péntek M (2019): A comparison of European, Polish, Slovenian and British EQ-5D-3L value sets using a Hungarian sample of 18 chronic diseases. European Journal of Health Economics 20, Suppl. 1, pp. 119-132. doi: 10.1007/s10198-019-01069-8.

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Rencz F, Poór AK, Péntek M, Holló P, Kárpáti S, Gulácsi L, Szegedi A, Reményik É, Hidvégi B, Herszényi K, Jókai H, **Beretzky Zs,** Brodszky V (2018): A detailed analysis of 'not relevant' responses on the DLQI in psoriasis: potential biases in treatment decisions. Journal of The European Academy of Dermatology and Venereology, 32, 5, pp. 783-790. doi: 10.1111/jdv.14676.

**Beretzky Zs**, Péntek M (2017): Informális ellátás és meghatározó tényezői krónikus betegségekben: magyarországi kutatások összehasonlító elemzése [Characteristics and determinants of informal care in chronic diseases in Hungary: a comparative analysis]. Orvosi Hetilap, 158, 52, pp. 2068-2078. doi: 10.1556/650.2017.30894.

**Beretzky Zs**: Az informális ellátás költsége krónikus betegségekben: magyarországi kutatások összehasonlító elemzése. Köz-Gazdaság, accepted for publication

Péntek M, **Beretzky Zs,** Brodszky V, Szabó, A. Kovács, L. Kincses, Á. Baji P, Zrubka Zs, Rencz F, Gulácsi L: A magyarországi lakosság egészséggel összefüggő munkaképessége: keresztmetszeti reprezentatív felmérés a Munkaképességre és Tevékenységcsökkenésre vonatkozó kérdőívvel. Orvosi Hetilap, accepted for publication

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