Corvinus University of Budapest
Doctoral School of Business and Management

Transferability of Productivity Loss Costs in Non-Communicable Diseases: Local Factors and Regional Adjustments

Ph.D. Dissertation

Healthcare Management

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LIST OF ABBREVIATIONS

ANOVA	Analysis of variance
BIA	Budget impact analysis
BoD	Burden of disease
CBA	Cost-benefit
CCA	Cost-consequence/ cost-outcome analyses
CEA	Cost-effectiveness
CEE	Central and Eastern Europe
CI	Confidence Interval
CMA	Cost-minimisation
CoC	Cost comparison studies
COI	Cost-of-illness
CUA	Cost-utility analysis
DALY	Disability-adjusted life year
ErC	Efficacy studies reporting costs
GCC	Gulf cooperation council
GDP	Gross domestic product
HCA	Human capital approach
HCI	Human capital index
HE	Health expenditure
HRQoL	Health-related quality of life
HTA	Health technology assessment
LMICs	Low- and middle-income countries
MENA	Middle East and North Africa
NCD	Non-communicable disease
PL	Productivity loss
QALY	Quality-adjusted life year
QHES	Quality of health economic studies instrument
SDG	sustainable development goals

V4	Visegrád four group
WHO	World health organization
WPAI	Work Productivity and Activity Impairment

I. INTRODUCTION

When common individuals are asked about the costs of their illness, they often think of the directly incurred costs such as medical, diagnostic or treatment fees, rather than their lost productive time or output, incurred due to their underlying illness. Although such costs might seem minor at an individual level, yet from a societal perspective the collectively lost production output can potentially comprise a significant chunk of the economy. The impact is amplified or contracted depending on various factors, among which is the disease's nature; for instance, in infectious diseases, such societal costs can be considered minor given the -relatively- short morbidity period during which the patient population is impacted. However, this impact is magnified in chronic illnesses (e.g. diabetes, low back pain, asthma) as those illnesses are often persisting for the rest of the individual's life.

Non-communicable diseases (NCDs) have been recognised to be one of the major challenges hindering countries face in their efforts to reach their sustainable development goals (SDG) (Horton, 2013). NCDs are chronic conditions requiring prolonged, expensive treatment regimens that adversely affect national revenue, socio-economic welfare, and economic growth, both directly (through medical and non-medical treatment costs) and indirectly due to productivity losses of patients as well as their carers (D. E. Bloom et al., 2012). Although these days -provided the current advanced medical knowledge and interventions- we can considerably mitigate NCDs' economic impact, yet due to the associated hefty price tags of those advanced interventions, coupled with the underestimation/exclusion of diseases' societal costs; such interventions can seem expensive falling beyond reimbursement thresholds. Direct treatment costs are only expected to keep increasing with the continuous development of the expensive, yet effective biologic agents (Cheng & Feldman, 2014). This has been placing an increasing pressure on policymakers to reimburse the most cost-effective health intervention while assuring future societal welfare.

Productivity is a measure of output per unit of input (Zhang, Bansback, & Anis, 2011). In health sciences, productivity loss (PL) refers to the individual's forgone output due to a health issue corresponding to the reduced output compared to a healthy individual. Recent years have seen

considerable attention towards the adoption of a societal perspective in health economic evaluations (Brennan, Perola, van Ommen, Riboli, & Consortium, 2017). The inclusion of the societal costs into health economic evaluations can better inform policy and health decision-makers toward maximising national social welfare, even if entry costs might fall outside the annual healthcare budgets (Krol & Brouwer, 2014). Krol and Brouwer (2014) demonstrated that productivity loss costs can potentially be higher than the associated direct medical costs. In such scenarios, a societal perspective is ought to be mandated as the traditionally considered direct disease costs for resource allocation are often insufficient for informed reimbursement decisions. The importance of investigating PL costs in this domain stems from the fact that NCDs account for over 70% of global mortality with most of those deaths happening in low- and middle-income countries (LMICs), significantly impeding the national collective output (Organization, 2018). In LMICs, the issue of the inclusion and exclusion of indirect costs/PL costs can be involuntary given the shortage of specialised experts in Health Technology Assessment (HTA), as well as their underdeveloped healthcare tracking infrastructure, which contributes to the scarcity, inaccuracy, and underutilisation of local health economic evidence (Ahmad Fasseeh et al., 2020).

While HTA generally mandates a societal perspective for informing reimbursement and resource allocation decisions, the bulk of the health economic evaluations -which are the building blocks of HTA- often adopt a narrow health system perspective. Although a societal perspective in health economic evidence is still not mandatory in most countries, yet some developed health systems have already started mandating a societal perspective for their reimbursement decisions (Krol & Brouwer, 2014). While In Belgium and France, such evaluations are mandated only in certain cases for public reimbursement (Krol, Papenburg, Koopmanschap, & Brouwer, 2011), yet in the Netherlands, their updated pharmacoeconomic guidelines five years ago mandated the conduction of health economic analysis from a societal perspective and further expanded to specify the valuation and estimation methods to be used (Versteegh, Knies, & Brouwer, 2016). Given the projected substantial economic and human capital welfare growth from such implementation, more countries are expected to follow and start mandating a societal perspective in health economic evaluations for reimbursement decisions.

The Middle east north Africa (MENA) region although comprising a variation in income levels, yet the region as a whole is suffering from typical LMICs symptoms of data, experts, and evidence scarcity (Ahmed M. Soliman, 2013; Sinaa A Al-Aqeel, 2012; Hammad, 2016). On the other hand, the economic evidence from the Visegrád Four (V4) region has been running for a longer time, and the science is expected to be -relatively- mature compared to the MENA. Although transferability of health economic evaluations can seem like a simple solution for data scarcity, yet methodological diversity, non-standardisation as well as the specificities of each disease are some of the factors contributing to the complexity of the costs' transferability across countries. Following a similar context, Muka et al. (2015) highlighted that NCDs present a huge financial strain on national economic prosperity, and emphasised that standardised methods for evaluating the economic impact of NCDs globally are crucial to enable consistency and transferability.

This work aims to demonstrate the socio-economic value of lost patients' productivity due to NCDs and provide a reference for future utilisation and transferability of PL costs from the V4 into the MENA region. We chose to work specifically with the V4 given the converging local variances in income levels, reimbursement capacity as well as the recent experience of member countries in HTA development and institutionalization. We use HTA as a proxy for the awareness and progression level towards the adoption of a societal perspective by systematically exploring the contrast in HTA scientific output between the MENA and Central and Eastern Europe (CEE). Our sub-aims bifurcated later on given the identified specific regional needs in order to reach our transferability aim.

Data scarcity from the MENA region dictated systematically mapping the health economic evidence allowing us to create a comprehensive MENA PL costs catalogue, facilitating assessment and transferability of PL costs. On the other hand, given the relative abundance of health economic research from the V4 region, we aimed to locally identify and rank NCDs PL impact as well as their significant PL drivers in order to be able to propose a simplified method for transferring PL

cost estimates cross-regionally, utilising economic indicators corresponding to our identified PL drivers. In each of the chapters, I contextualise the research goals based on previous work and literature in light of my aims. Figure 1 below illustrates the research framework adopted in this dissertation.

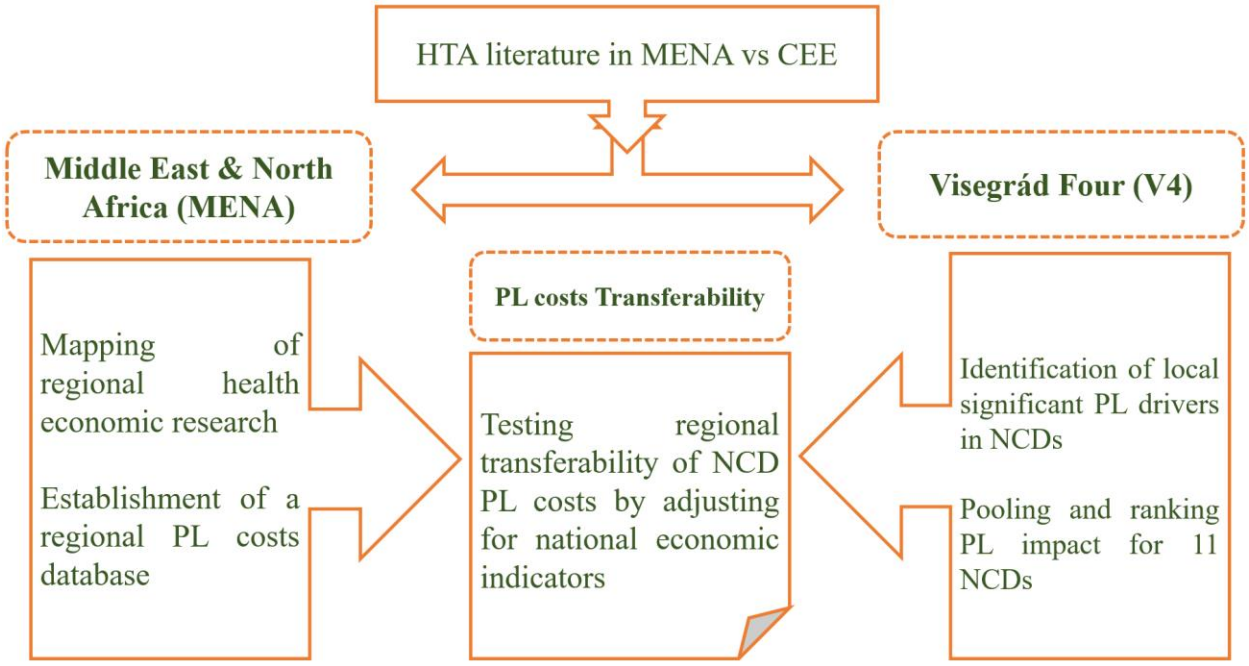


Figure 1. Dissertation's research framework.

II. CHAPTER: LITERATURE REVIEW

II.1. Non-communicable Diseases (NCDs) and socioeconomic burden

NCDs differ from other diseases in the sense that they do not transfer from one patient to another through an infectious route. They include a broad range of chronically extending illnesses, such as cardiovascular disease, diabetes, obesity, mental and musculoskeletal disorders. These illnesses pose detrimental health implications for patients, their families, societies, and further threatens to strain healthcare systems (Unwin & Alberti, 2006). The associated socio-economic costs of NCDs make the prevention and control of these diseases a major development priority for the 21st century as highlighted by the WHO (Organization, 2018). Current measures of the prevention and control of infectious diseases, the advancement of medical science and expertise, along with the development of health and social structures, have all collectively contributed to increasing life expectancy among many other health indicators. While this alone is a noteworthy achievement, yet the resulting epidemiological and socio-demographic shifts (e.g. age distribution) also mean that the burden of NCDs will consequently increase given their high late age prevalence (Division, 1999).

Longer life expectancy leads to a greater elderly population with a higher risk of chronic health issues. A societal perspective in assessment is more important than ever given the need to make the most out of scarce resources and to achieve the greatest societal benefit in reimbursement decisions. NCDs deprive people of their full productivity and economic capacity. From a national perspective, NCDs decrease the quality, life expectancy, and consequently the total economic output. Abegunde and Stanciole (2006) highlighted channels through which such productivity losses can happen due to NCDs; higher dependency ratio (informal care), diminished labour productivity, reduced access to production factors, reduced capital savings, and purchasing power. All these channels together can also discourage foreign direct investments (FDI) in the country concomitantly decreasing the economic growth while widening social inequalities and increasing poverty. Due to those aforementioned reasons, NCDs will be the concentration in this work as

their associated factors and results transferability will have a substantial positive impact on social welfare.

II.2. Health Technology Assessment (HTA)

HTA is the comprehensive, multidimensional evaluation of the impact of a health technology where both the direct and indirect effects of a certain health technology are valued and monetised, to better inform decision-makers in priority setting and public health reimbursement decisions (Dankó, 2014; Organisation, 2020). Health technologies are the result of knowledge and applied skills to form a device, medicine, vaccine, procedure, or a system designed to reduce the burden of a certain health issue or improve an individual's quality of life (WHO, 2007).

Although HTA institutionalisation -as a dedicated entity- is not established in most countries due to many constraints such as the lack of local expertise or insufficient funding; yet, around the world, sub-specialized assessment units – which can be considered as an HTA seed- are starting to emerge around the globe, especially in financially less capable economies. This is partly due to the gradual realization that old reimbursement and assessment methods for health interventions no longer capable of providing the most cost-effective decisions in many cases, especially where a societal impact is significant such as the case with NCDs. Those sub-specialized units are usually established within an institution (such as a major hospital or university) or in health ministries. An example of such units are the health and Pharmacoeconomics units which do undertake or utilise economic evaluations for reimbursement decisions. Although these sub-entities do add tremendous value to the decision-making process, yet their impact is still far from the full institutionalisation outcomes especially that their recommendations are often still not mandatory informal, non-binding, lacking ethical assessment, or not publicly transparent, violating key HTA aspects which renders their functionality ineffective.

HTA in the MENA region is still in its initial phases since the region still relies on other (i.e. non-value based) pricing and valuation methods, most commonly, External Reference Pricing (ERP) as most LMIC do. ERP is one of the simplest and oldest medical pricing tools and is sporadically

employed in the MENA by benchmarking prices against the lowest list price in reference countries (Maskineh, 2018). In the EU however, in western EU to be specific, HTA application and institutionalisation are ahead compared to less capital-rich countries provided the diversity in health systems development and financing capacities among member countries. The Central and Eastern European (CEE) countries have shown considerable recent advancement in the field of HTA and are on their way into a full HTA utilization capacity, although at different speeds.

Given the sporadic relative similarities in income levels, reimbursement capacity as well as the recent experience of the CEE countries in HTA development and institutionalisation, we chose the CEE region as a reference point in HTA assessment against the MENA region. HTA research can be considered a good proxy of the level of socially inclusive health economic research, as they are often mandated in HTA reimbursement decisions. Moreover, the generation of HTA reports requires high-quality economic evaluations which can be an asset concerning the international transferability of the results. In chapter IV, we identify HTA related literature from the CEE and compare it to HTA research output in the MENA region. We conduct such a review to help map and give direction on specific needs for each region in light of our transferability target.

II.3. Health economic evaluations

Health economic evaluations are considered the building blocks of HTA since they address the costs associated with the intervention on hand. Many types of health economic evaluations exist, for instance, Cost-of Illness (COI) studies simply assess the costs associated with a single disease or a domain of illnesses (e.g. NCDs). While on the other hand, comparative evaluations such as cost-effectiveness analysis (CEA) compares both the costs and effectiveness of two interventions intended for the same patient population and present the results in terms of cost-effectiveness. Both are equally important to aid decision-makers in resource allocation and reimbursement decisions and both are reliant on each other.

Health economic evaluation types can be split into two domains (M. F. Drummond, Sculpher, Claxton, Stoddart, & Torrance, 2015); full and partial health economic evaluations. Full economic

evaluations are comparative analyses of alternative courses of health intervention covering both health costs and outcomes. While on the other hand, partial economic analyses focus solely on either costs or effectiveness and do not usually involve a comparison of alternative courses. Full economic evaluations investigate both outcomes and costs and include cost-utility- (CUA), cost-effectiveness- (CEA), cost-benefit- (CBA), cost-minimisation- (CMA), and cost-outcome/cost-consequence analyses (CCA)). CEA is a comparison of costs in monetary units with outcomes in quantitative non-monetary units (Towse, Pritchard, & Devlin, 2002) while CUA is a form of cost-effectiveness analysis that compares costs in monetary units with outcomes in terms of their utility (e.g., in quality-adjusted life years (QALYs)), CCA also is a form of cost-effectiveness analysis which presents costs and outcomes in discrete tabular categories. CBA compares costs and benefits, both of which are quantified in common monetary units.

On the other hand, partial economic evaluations mainly include evaluations involving either costs or consequence Contrary to comparative full health economic evaluations which assess and compare the effects of a different health intervention (Brown, Lipscomb, & Snyder, 2001).; Budget impact analysis (BIA), Cost-of-illness (COI), cost comparison studies (CoC), as well as efficacy studies reporting costs (ErC), are all considered as partial health economic evaluations; BIA estimates the monetary consequences of adopting a new intervention from a health system perspective, and is usually done alongside CEA. Burden of disease (BoD) and COI studies are often used interchangeably and encompass various aspects of the disease's impact on the health outcomes and costs. In our work, we distinguish between the two in the sense that COI studies aim to quantify all the costs of a specific disease by capturing the value of the resources spent or lost as a result of that underlying health issue. While Burden of disease (BoD) studies report both costs and outcomes of a certain disease. CVP accounts for costs that impact different levels of consumption volume adjusting for operating profit, although it is rarely utilized in health economic evaluations as it -often- concerns manufacturers rather than health systems. Table 1 illustrates the main types of full and partial economic evaluations as referred to in this work.

Table 1. Full and Partial health economic evaluations and their corresponding abbreviations.

Full economic evaluations	Partial economic evaluations
cost-utility analysis (CUA)	Budget impact analysis (BIA)
cost-effectiveness analysis (CEA)	Cost-of-illness (COI)
cost-benefit analysis (CBA)	Burden-of-Disease (BoD)
cost-minimisation analysis (CMA)	Cost comparison studies (CoC)
Cost-outcome/Cost-consequence analyses (COA) / (CCA)	Efficacy studies reporting costs (ErC)

II.4. Types of disease costs

Disease costs typically originate from three sources; first are the directly incurred costs on both the health system and the patient and are referred to as "direct costs". on the other hand, "indirect costs" are the costs incurred on the patient and/or their caregiver, due to their impaired or decreased productivity due to the illness. Direct costs can also be split further into direct medical costs (e.g., medical administration, medications, hospitalization, out-, and in-patient visits) and direct non-medical costs (e.g., professional home help, transportation costs). While indirect costs measure productivity losses borne by the patient (whether paid or unpaid) and his carers (caregiver/household income loss) and employer, all collectively impacting society's economic welfare. "Intangible costs" are a third cost category that is concerned with the costs of pain, suffering, and the decrease in overall quality of life and life satisfaction due to the disease. Those costs merely depend on the willingness to pay concept (WTP), and are scarcely addressed in health economic evaluations due to the difficulty in accurately measuring and thus quantifying such costs in monetary terms (Hodgson & Meiners, 1982; Segel, 2006). Our concentration in this dissertation will be targeted towards the indirect costs associated with illnesses. Figure 3 illustrates these types of disease costs.

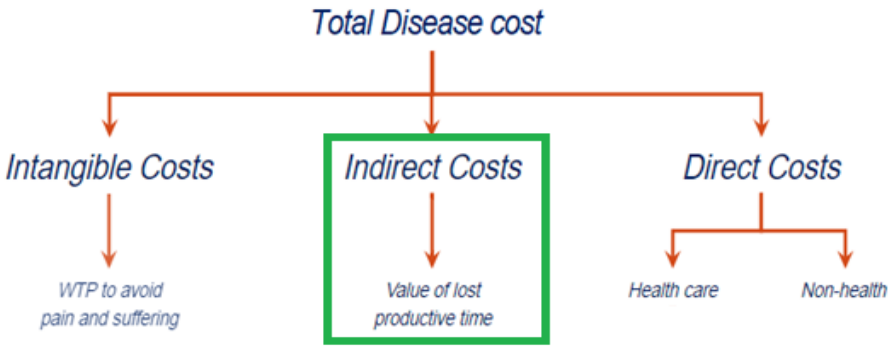


Figure 2. Types of disease costs schematic.

II.5. Productivity Loss (PL) costs

To address the role of PL in health economic evaluations, we first need to describe the arms from which an individual's productivity due to a disease is lost. Zhang and Anis (2014) discriminated between two major PL categories:

A. Paid activities:
   - People who lost their employment suddenly due to premature death (i.e., mortality).
   - People who are maintaining employment concurrently with the disease (i.e., morbidity)
     - Increased sick leaves and absences (absenteeism).
     - Reduced routine work time (short- and long-term disability).
     - Reduced typical productivity levels at work (presenteeism).
     - Premature retirement.

B. Unpaid activities: These are the productive activities that fall outside of the common labour market such as household work (e.g. house chores, grocery shopping), care work (e.g. taking care of family children, personal care), and volunteer work (e.g. community center volunteering) (Krol & Brouwer, 2014). It is important to discriminate between leisure time and unpaid activities; although leisure time is of significant mental and physical health value, yet it does not directly impact the societal economic output, and is often categorised as direct non-

medical cost (A Fasseeh et al., 2018). One way of differentiation is that if those unpaid activities are those activities that are replaceable by a third person/market substitute, then those activities are accounted for as indirect PL costs (Krol, 2012). PL cost types are summarised in table 2.

As highlighted above, paid activities PL is the resulting economic deficit either from complete absence from work (i.e., Absenteeism) or from working under sub-par conditions due to disease compromising output's quality or quantity (i.e., presenteeism). Depending on the disease nature, presenteeism might be of significant or insignificant economic value. For instance, Ricci et al. (2005) demonstrated that in the US, rheumatoid arthritis patients experience even higher presenteeism costs than absenteeism. This is due to the physically and mentally exhaustive nature of musculoskeletal disease on patients as well as their caregivers. In such scenarios, PL calculations based on absenteeism solely can (in some cases) reflect an incomplete cost estimate, consequently misleading decision-makers in budget allocation (Krol & Brouwer, 2014).

PL costs also apply to the caregivers and/or the households who care for the patient and are often referred to as informal care. For certain intensively compromising chronic illnesses (e.g., dementia, schizophrenia); patients' self-reliance is considerably compromised for average daily life tasks (e.g., grocery shopping on their behalf, cleaning, medical visits escorting). In these scenarios, a caregiver is required to assist the patient in his daily life tasks. When informal care is considered as a proxy of home/domestic help and is provided by the system, it is categorised as direct non-medical costs. However, when the opportunity of lost caregiver's work and/or leisure time is valued using the opportunity cost method, they are categorised as indirect costs relating to the caregiver's PL. The opportunity cost method attempts to place a monetary value for the alternative use of the carer's time (Costa et al., 2013).

Morbidity costs are the lost wages from individuals who became unable to work fully or partially because of disability, directly connected to a specific illness (paid). Morbidity costs also include the value of lost capacity of ill individuals to perform their basic daily life work (unpaid). Mortality

costs on the other hand are the current value of the future earnings projected to be lost by premature death (Rice, Hodgson, & Kopstein, 1985).

Table 2. Patient's PL cost types due to illnesses.

Paid activities					**Unpaid activities**
Mortality	Morbidity				Non-labour market activities (i.e. replaceable by a third person)
Premature death due to disease	Long- and short-term work disability	Premature retirement	Absenteeism (e.g. sick leave/absence)	Presenteeism (i.e. decreased work output during work hours)	e.g. Household work, caregiving work, volunteer work

II.6. PL measurement

To assign value to patients' productivity, we need to be able to measure it as it is commonly said "You can't manage what you can't measure". The impact of illness on the patient's workability is often quantified using standardized questionnaires such as the "Work Productivity and Activity Impairment Questionnaire" (WPAI) and validated to fit illnesses. WPAI is a self-reporting instrument developed to measure patients' PL due to a health condition covering both paid (absenteeism and presenteeism) and unpaid work time lost due to the underlying illness (Reilly, Zbrozek, & Dukes, 1993). Health and Labour Questionnaire (HLQ), iMTA Productivity Cost Questionnaire (iPCQ) and Valuation of Lost Productivity (VOLP) are other validated tools used to measure PL (Krol & Brouwer, 2014). These validated tools also differ in the way they measure PL; for instance, WPAI, HLQ, and HPQ instruments provide results in direct monetary costs, while other instruments provide results in non-monetary terms which are not preferred by health decision-makers (Kigozi, Jowett, Lewis, Barton, & Coast, 2016; Mattke, Balakrishnan, Bergamo, & Newberry, 2007).

To give further insight, these productivity assessment tools typically start by asking questions laying the background about the patient's job whether if it's paid or unpaid, the number of usual

working hours, their age, gender, and gross wage if working. The number of days completely missed by the patient from work due to the health issue under investigation is recorded and is referred to as "absenteeism". Similarly, the number of days when the patient was at work suffering from that health issue along with the magnitude of the impact is further recorded and is referred to as "presenteeism" (Krol et al., 2011). The biggest obstacle in calculating presenteeism is the lack of a gold standard or objective tests to assess the validity of the criterion as they are reliant on self-assessment by the patient. some objective tests are available only for limited occupations and industries (Zhang & Anis, 2014). However, previous work has demonstrated that they provide a tangible proxy for decision-makers in priority settings (Scuffham, Vecchio, & Whiteford, 2014). Standardisation and validation of such assessment tools are key to robust PL costs transferability.

II.7. PL monetisation

As for the monetary imputation of PL, minor differences are present between the monetisation of paid and unpaid work. For paid work, two valuation approaches are often used, i.e. the human Capital Approach (HCA) and the Friction cost approach (FCA). The human capital approach simply calculates the productivity loss by multiplying the working hours lost due to the health issue with the gross hourly wage of the patient regardless of the period of absence (in case of absenteeism). The friction cost approach on the other hand measures the time required to hire and train another healthy person who can fully replace the patient's position; so even if the patient is absent for a long time, after a certain point defined as (friction period) the PL valuation will not increase any further than the money and time spent to replace the ill worker during that friction period.

It is important to note that in the case of long-term absences of patients, the HCA will generate higher PL numbers on a monetary basis. While alternatively, FCA assumes that an ill individual can ultimately be replaced by a healthy substitute which can take a certain amount of time and training investment, which are both translated into an assigned friction period cost -over which- minimal extra costs apply. Although the choice between the methods is dependent on the health system structure, yet HCA is often considered the method of choice by most researchers in the region as will be shown in the results section. FCA method ignites much controversy; for instance,

an issue arises when the patient is healthy again after successful treatment and recommences his workstation. The costs associated with two individuals doing the same job in case a replacement has been assigned already, and nevertheless the time and money spent on training the replacement are not accounted for. Although some researchers proposed a 0.8 multiplication elasticity factor when adopting the friction cost approach -since the reduced labour time is assumed to naturally give a bit less than proportional production- yet, the factor itself can be challenged as well which is the reason why the elasticity factor is often not used in FCA by most researchers (Krol & Brouwer, 2014). This controversy is out of our current scope and is further discussed by other researchers (Slomp & Molleman, 2002).

On the other hand, M. F. Drummond et al. (2015) suggested two main valuation approaches for unpaid PL; opportunity cost and replacement cost approaches. In opportunity cost approach, the time value lost due to health issues is calculated based on the market's net average wage for the same period of individuals' age, gender, and educational level (as best estimate or proxy). On the other hand, the replacement cost approach simply calculates the output value achieved by an equivalent monetary market service, in other words, it is based on the net wage for a market substitute for the foregone activity, such as a babysitter wage as an equivalent to time spent with family children (Zhang et al., 2011). Table 3 below gives a summary of the common PL monetisation methods for PL.

Table 3. Common PL monetisation methods.

Paid activities		**Unpaid activities**	
HCA	FCA	Opportunity cost	Replacement cost

II.8. Health status and PL

The relationship between the current health status of the patient and PL is undeniable; the better the patient feels, the higher the productive capacity. This has been proven empirically by many authors such as (Mitchell & Bates, 2011). To test for the association between the overall health

state of the patient and PL, health status needs to be initially measured. Different measurement tools have been developed and questionnaires are considered the most common tool to gather information needed for the patient's health status quantification. Standardised questionnaires (such as EQ-5D-3L/ EQ-5D-5L) are currently well developed and are being translated into different languages to fit diverse, international, patient populations, minimising international bias and contributing to the standardisation of the health status measurement.

EQ-5D-*L is a group of instruments used to provide a perception of the current health state, and has been used and validated in many disease areas over the past 30 years (Devlin & Brooks, 2017). Different versions assess different dimensions, and it is the health status tool of choice recommended by many HTA organizations (Mukuria, Rowen, Hernández-Alava, Dixon, & Ara, 2017). The EQ-5D-3L version (which will be in focus for this dissertation) measures three levels of health problems for 5 health dimensions. Health problems are denoted by (1: no, 2: moderate, 3: severe) and the five health dimensions are (self-care, mobility, usual activities, anxiety/depression and pain/discomfort). Hence, these levels with the dimensions together describe 243 (3^5) discrete health states (Group, 1990). In disease PL assessment, we hypothesise that a higher health status score is significantly correlated with lower PL. This hypothesis will be tested specifically for NCDs in chapter VII (H3).

II.9. PL transferability

Provided the locality of research funding, most health economic evaluations are often done for a single country or region. Conducting local specific health economic evaluations for each disease population is both time and money consuming and is probably out of reach for most countries. Due to the pressure to deliver the most cost-effective interventions while maintaining precise health budget distribution; decision-makers frequently face the question of whether international costing and evaluation results can be directly implemented into their local setting, adjusted or whether they need to undergo a new specific national study. Transferability refers to implementing the outcomes of international research in one country with/without modifications into another (Gao, Hu, Zhao, & Li, 2016). Transferability checklists have been proposed by many researchers and organisations. Goeree et al. (2011) carried a systematic review to identify novel international

transferability checklists for health economic evaluations. In their conclusion, they identified seven novel articles proposing a unique system or checklist/chart to assess the geographic transferability of the results. Most of those checklists included a smaller subset of variables which included the most critical factors to consider, facilitating results transferability assessment. However, those tools were designed for higher capacity research where health economic guidelines are fairly followed. In developing regions such as the MENA, the scarcity of sufficient local expertise will only contribute to decreasing the overall quality of research thus, often failing the transferability checklists. In the CEE, Mandrik, Knies, Kalo, and Severens (2015) reviewed the health economic evaluations from eastern Europe and found that only 36% of the studies discussed or addressed the transferability of their results.

Many researchers have addressed the causes behind the results generalisability issue; Knies, Severens, Ament, and Evers (2010) showed that the complication in building health economic model arises during the different stages of construction; the first discrepancy starts due to the lack of consensus on the inclusion of societal costs. Moreover, the jurisdiction also impacts the costs identification and quantification methods. In North America, the preferred costs identification method is the "Quality adjusted life years" (QALYs), while the rest of the world -with minimal exceptions- prefers the identification of costs using direct monetary terms (e.g. USD, EUR, PPP). Moreover, when either identification direction is adopted, specific patient population or costs may or may not be all included (e.g. paid vs. unpaid, absenteeism, presenteeism, disability) which is also an extra hurdle for international results transferability. The same methodological discrepancy goes on as we go further into the model. The valuation method adopted for the patients incurred costs (e.g. HCA, FCA), as well as the data source used in the model (e.g. patient-reported questionnaires, hospital database, insurance database) only further contributes to widening the results transferability and comparability both internationally and locally.

Transferability factors of health economic evaluations were assessed by a few researchers. Welte, Feenstra, Jager, and Leidl (2004) systematically identified three major domains where these factors fall into; Methodological characteristics, Healthcare system characteristics, and human capital characteristics. In direct disease costs, the often-large disparity between health care systems, such

as the variance in patterns of clinical practice (e.g., variation in hospitalisation rate, therapeutic guidelines, alternative therapies) as well as specific jurisdiction costs, accurate transferability of direct costs can be far-fetched. In an attempt to provide an international transferability method for direct medical costs, Gao et al. (2016) proposed a feasible empirical approach by pooling and converting the direct costs into a percentage of the local GDP/capita, and used it as a proxy estimate approach for the international transferability of direct medical costs for three NCDs (i.e. diabetes, epilepsy, and schizophrenia). On the other hand, Indirect costs transferability is less addressed than direct costs in the literature. Zhao, Xie, Hu, and Li (2013) explored the factors contributing to the variation of indirect cost and tested the feasibility of transferring indirect costs across jurisdictions in a similar manner. The authors used quantitative modelling methods to identify significant variables contributing to variance in indirect costs and proposed that results adjustment as a proportion of GDP/capita provided less variance in results than the unadjusted cost terms. This might be explained by the varying national economic output, local human-capital output as well as health spending capacities among other factors.

II.10. Human Capital Index (HCI)

Ul Haq (1995) defines human capital as the collective resources of knowledge, talent, skills, abilities, experience, intelligence, judgment, and wisdom, that are attained both individually and collectively as a society. All these resources combined indicate the capacity of people to work towards wealth generation. The Human capital index (HCI) is a recently developed indicator for national societal output. The idea behind the HCI is linked with the concept of human resource management in business and economic practices and can have an indicative role in the projected national productivity growth, economic development, and innovation (Barro, 2001). Generally, the index considers three major national aspects; standard of living, education, and health to devise an index value indicating national prospective productivity.

Significant resource gaps in human capital resources exist between nations. The world bank launched the Human Capital Project harvesting efforts to address these gaps by raising awareness about the costs of underperforming human capital (Bank, 2018). In this regard, the HCI was created to assign value for collective economic productive capacity. HCI is a global parameter that scales

the key components of human capital across different domains. It helps the government and economy experts to measure and estimate what children born today, in a certain country or population, can expect to produce by the age of 18. Adjustments for national gender inequality and workforce utilization (UHDI) have also been introduced and incorporated for more accurate projections (Kraay, 2019). Although it might seem that HCI can serve as a good tool for the adjustment and transferability of human capital output between different geographical locations, few researchers have tested its potential in international PL costs transferability. In chapter VIII, we test the feasibility of using the HCI as an adjustment factor to minimise international PL costs transferability.

III. RESEARCH HYPOTHESES

The following hypotheses were tested concerning each chapter's aim in light of our final goals:

1. In chapter V, we systematically map the current health economic research trends in the MENA region, during which we test:

   - *H1: Given the superior financial capacity in high-income countries, we assume that their group will comprise the highest share of full economic evaluations from the MENA region. (Methods:44, Results: 48) - Rejected.*

2. In chapter VI, we comprehensively identify all PL costs from the MENA region and report them in a cost library facilitating PL costs transferability, during which we test:

   - *H2: Among the MENA studies reporting societal perspective costs, we assume that there is a significant association between country income groups and investigated ICD-10 disease groups. (Methods:55, Results: 59) – Accepted.*

3. In chapter VII, we proceed with pooling NCD PL costs to identify significant local PL drivers and NCDs with high impact, during which we test:

   - *H3: Health status and educational level have a significant impact on musculoskeletal disease PL costs. (Methods: 66, Results 73) – Accepted.*

4. In chapter VIII, we provide a regional average for musculoskeletal disease PL costs for the V4, and we test different transferability methods, during which we test:

   - *H4: We assume that cross-country PL cost differences are negligible among the V4, provided similar social and economic welfare. Hence, insignificant differences in PL cost estimates are expected within the region. (Methods: 86, Results 90) – Accepted.*

- *We assume that incorporating the national Human capital index (HCI) as an adjustment factor can aid in generating more precise PL estimates interregionally than sole GDP/capita adjustment. (Methods: 86, Results 94) – Accepted.*
- *H6: we assume that adjusting for health expenditure (HE) as an adjustment factor can aid further in generating more precise international disease cost estimates when coupled with GDP/capita. (Methods: 86, Results 94) – Rejected.*

IV. CHAPTER: HEALTH TECHNOLOGY ASSESSMENT (HTA) BETWEEN THE MIDDLE EAST AND NORTH AFRICA (MENA) AND CENTRAL AND EASTERN EUROPE (CEE) REGIONS: A SCOOPING ANALYSIS OF LOCAL RESEARCH

This subsection is partially based on the published conference proceeding (Rashdan & Alshafeey, 2019) and I further expand to include the MENA region data to set a contrast between the regions.

Rashdan, O., *& Alshafeey, M. (2019). HTA in CEE Countries: A Bibliometric Analysis of Research. In Proceedings of FIKUSZ Symposium for Young Researchers (pp. 192-203). Óbuda University Keleti Károly Faculty of Economics.*

In this chapter, our aims were exploratory to aid in setting region-specific goals. Using Health Technology Assessment (HTA) as a proxy, we evaluate the progression of societal perspective adoption in health economic research. We used unified, systematic methods to conduct a literature review exploring the difference in the quantity and quality of publications addressing HTA from both the MENA and CEE regions to set region-specific goals towards the final transferability aim.

IV.1. Methods

Systematic literature search methods were used. Scopus database was selected given the ease of use, bibliometric data richness, and access to high-quality peer-reviewed research. For the MENA region, we included seventeen countries i.e. Algeria, Bahrain, Egypt, Iraq, Jordan, Kuwait, Lebanon, Libya, Morocco, Oman, Qatar, Palestine, Saudi Arabia (KSA), Syria, Tunisia, the United Arab Emirates (UAE, including Dubai and Abu-Dhabi) and Yemen. While for the CEE region, we opted to cover CEE countries that were part of the former Eastern bloc given their comparable income level. We have selected the following nine CEE countries: Poland, Czech, Hungary, Romania, Bulgaria, Slovenia, Slovakia, Serbia, Croatia. For the CEE database we searched articles from inception till October 2019, while for the MENA database, we extend the search period up until December 2019.

The search code used both “HTA”, “Health Technology Assessment" by combining them with country keywords, and the two sets were varied using Boolean search operators “AND”, “OR”. The search was targeted for the title, abstract, or keywords fields, and was limited to journal articles, published in English language, with full-text available. The resulting articles title/abstracts were screened for eligibility by two independent authors (OR, MA), and any discrepancies were resolved by consensus. Table 4 shows the search code used.

Table 4. Scopus search code.

CEE region: (TITLE-ABS-KEY ("HTA" OR "Health Technology Assessment") AND TITLE-ABS-KEY ("Poland" OR "Czech" OR "Hungary" OR "Romania" OR "Bulgaria" OR "Slovenia" OR "Slovakia" OR "Serbia" OR "Croatia")) AND (LIMIT-TO (DOCTYPE,"ar")) AND (LIMIT-TO (LANGUAGE,"English")) MENA region: (TITLE-ABS-KEY ("HTA" OR "Health Technology Assessment") AND TITLE-ABS-KEY ("Egypt" OR "Egyptian" OR "Iraq" OR "Iraqi" OR "Jordan" OR "Kuwait" OR "Libya" OR "Moroccan" OR " morocco" OR "Oman" OR "Qatar" OR "Saudi" OR "Syria" OR "Tunis" OR "United Arab Emirates" OR "Dubai" OR "Abu Dhabi" OR "Yemen" OR "Palestine" OR "leban")) AND (LIMIT-TO (DOCTYPE,"ar")) AND (LIMIT-TO (LANGUAGE,"English"))

Bibliometric variables used for this analysis were - the title of the article, the corresponding journal name, year of publication, author names, country affiliation, number of citations, and index keywords. Scimago journal ranking (SJR) was used as a rough indicator of the publication quality. Although the journal’s rank is not necessarily indicative of the paper quality, yet it is no doubt that higher-ranked journals have more strict guidelines which would ultimately lead to a greater proportion of high-quality articles overall. Thereof, each article was marked with its corresponding SJR rank, while taking into consideration the publishing year and the journal rank during that specific year. To enable such year-specific SJR identification, Microsoft Excel was used for database management, we compiled a large database of annual Scimago journal ranks (1999-2019) into one database. We then used the “vlookup” function to connect both databases and generate each article’s year-specific SJR. R studio equipped with “bibliometrix” R-package was used to

generate the scientific output per country, and SPSS 23 statistical software was used to test for significant SJR group mean differences.

IV.2. Results

Search results for our MENA countries gave 25 articles in total, while from the CEE we attained 107 articles. From the MENA results, we excluded a total of 21 out of 25; 6 were out of the study field (e.g. chemistry-related) and 15 were excluded since they were in French language. The final included articles from the MENA region were 4 publications, written by 25 authors, with the first published as recent as 8 years ago (2013-2019) and a total of 36 citations overall. None were single-authored. This indicates a weak, yet recent interest in the field of HTA from within the MENA. It is worth noting that all the excluded French-language articles were published in the same year (2015) for Algeria and none of them had any citation. Table 5 shows the final included articles from the MENA region.

On the other hand, for the CEE database, we have excluded 13 articles 7 that were out of our study field. The final number of articles included for the CEE region was 94 articles, which were written by 369 authors between the time period of 1995 and 2019, with an average of 3.93 authors per document and a per document citation average of 14.36. Only 6 articles were single-authored papers. Figure 3 shows the selection process flowchart for both CEE and MENA results. Table 6 shows the descriptives of the extracted CEE articles, while the 94 included articles from the CEE along with MENA search results are tabulated in appendix I (Supplementary table 1 and 2 respectively).

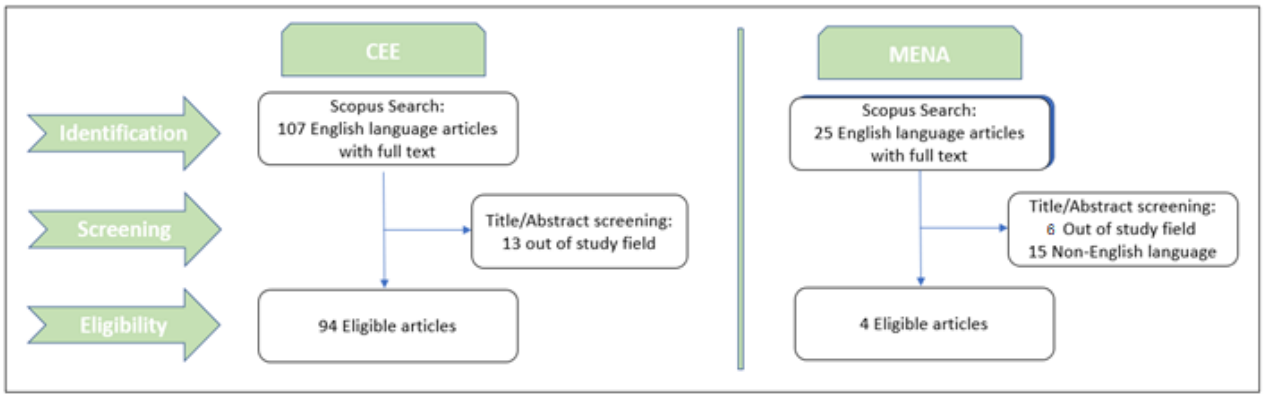


Figure 3 . Prisma flow diagram for our CEE and MENA search.

Table 5. MENA included publications.

Authors	Article Title	Journal name	publishing Year	Number of citations	SJR
Elsisi G.H., Kaló Z., Eldessouki R., Elmahdawy M.D., Saad A., Ragab S., Elshalakani A.M., Abaza S.	Recommendations for reporting pharmacoeconomic evaluations in Egypt	Value in Health Regional Issues	2013	19	Q3
Babigumira J.B., Jenny A.M., Bartlein R., Stergachis A., Garrison L.P.	Health technology assessment in low- and middle-income countries: A landscape assessment	Journal of Pharmaceutical Health Services Research	2016	14	Q2
Hayajneh W.A., Daniels V.J., James C.K., Kanibir M.N., Pilsbury M., Marks M., Goveia M.G., Elbasha E.H., Dasbach E., Acosta C.J.	Public health impact and cost effectiveness of routine childhood vaccination for hepatitis a in Jordan: A dynamic model approach	BMC Infectious Diseases	2018	2	Q1
Darawsheh B., Germeni E.	Implementing health technology assessment in Kuwait: A qualitative study of perceived barriers and facilitators	International Journal of Technology Assessment in Health Care	2019	1	Q2

Table 6. Overall characteristics of the CEE included studies (n=94). *Source: (Rashdan & Alshafeey, 2019)*

Description	Result
Timespan	1995 - 2019
Average citations per documents	14.36
Average citations per year per doc	2.3
Authors	369
Authors of single-authored documents	5
Authors of multi-authored documents	364
Single-authored documents	6
Documents per Author	0.255
Authors per Document	3.93
Co-Authors per Documents	5.11

IV.2.1. Active years, Journals, and SJR for CEE publications

Figure 4 shows the CEE articles by publication year, colour coded as per their corresponding SJR for that specific year. It can be noticed that most publications discussing the HTA topic were published in the 5 years with a significant output jump in 2016. This demonstrates the recent increased attention towards the HTA topic in the CEE region. With regard to journal quality, almost half (47%) of the total number of publications were published in Q1 ranked journals, 40% in Q2, and only 13% were published in Q3 and Q4 journals. This indicates that HTA is a hot topic as most of the HTA research is published in high-impact journals.

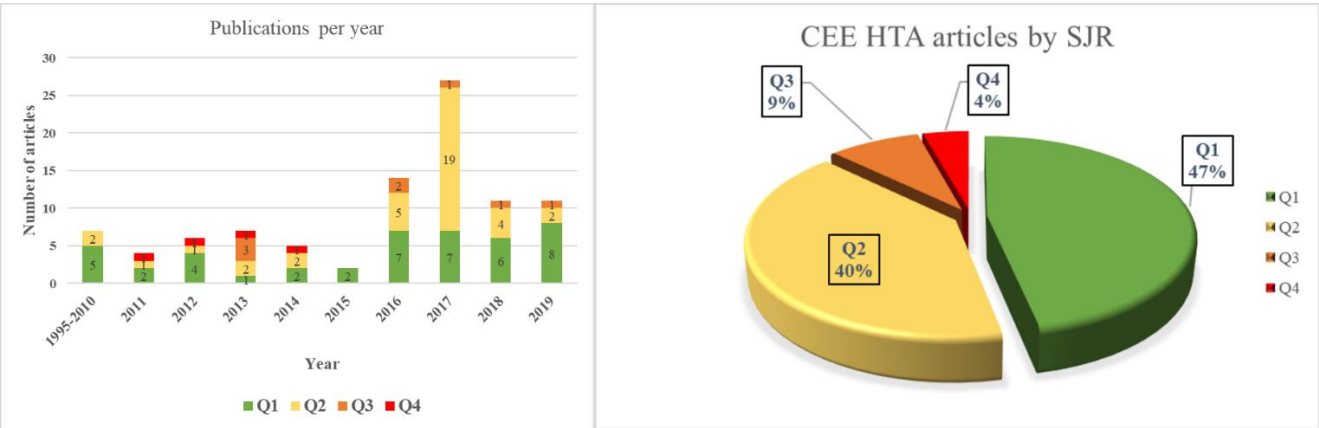


Figure 4. CEE HTA publications by year and SJR. *Source:(Rashdan & Alshafeey, 2019)*

The extracted articles from the CEE were published in 41 journals in total. Almost 30% of the journals published one article only, while 70% published two or more articles. This can shed light on the journal's specialty and direction. Among the top, the "International Journal of Technology Assessment in Health Care" has the highest number of publications (i.e. 17 publications), while the journals "Value in Health Regional Issues" and "Health Policy" have 13 and 11 publications, respectively. Almost 50% of the CEE articles were published in these top 5 journals shown in figure 5.

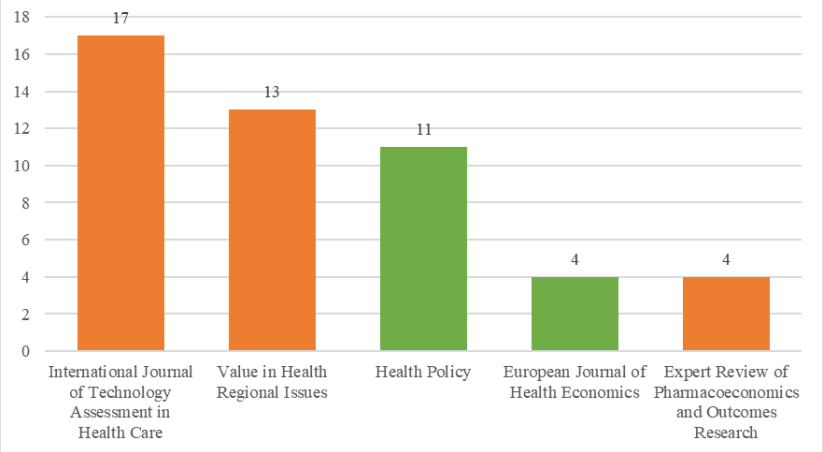


Figure 5. Top journals publishing about HTA for the CEE region color-coded as per their corresponding SJR. *Source: (Rashdan & Alshafeey, 2019)*

IV.2.2. Scientific output by country

The scientific output per country (frequency of the author's affiliation country) was investigated to give an idea of which CEE countries are the most active in publishing in the HTA field. Figure 6 shows the authors' affiliation country analysis result. Poland came on top as the most active country in HTA research with 84 affiliations publishing in the field, which makes over 19% of the total HTA publishing affiliations in the region. Hungary was among the top regional publishers contributing to nearly 14% of the total publications. Some countries outside the target regional population such as the UK, Netherlands, Germany, USA, Canada, and Spain were also active publishers for the CEE region. This indicates that HTA research in the targeted CEE countries is significantly reliant on international collaborations from experts from more advanced health systems. Poland's HTA system is one of the most established in the region with regular HTA reports released regularly and publicly. This reflected directly on the scientific output setting it ahead of the group with a minor edge over Hungary.

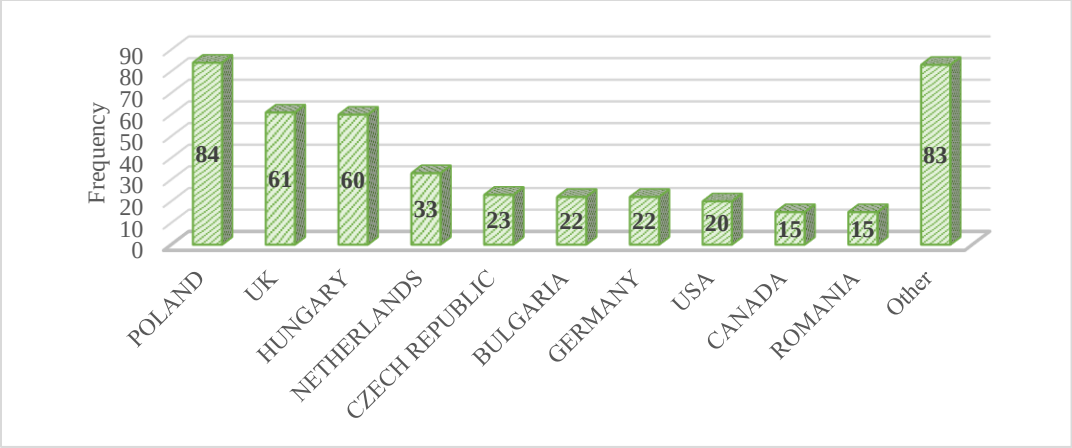


Figure 6. The scientific output of CEE by frequency of authors' affiliation country.

IV.2.3. Statistical analysis

Due to the small sample size in MENA, comparative regional statistical analysis was not sensible. However, ANOVA was employed to assess the relationship between the number of citations and the SJR in the CEE region. Table 7 shows our ANOVA results which indicate that there was no significant difference in the citations group means between SJR ranks. However, this result cannot be considered conclusive for two main reasons which are related to the limitations of this study; First is the small sample size, which contributes to the results inconclusiveness. The second reason is the lack of adjustment for the publication year as it is common sense that the older the article, the higher the chances for it to get cited. We did not build a model to adjust for the publication year provided the small sample size.

Table 7. ANOVA results of SJR and Number of citations for CEE region HTA research.

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	260.878	3	86.959	.104	**.958**
Within Groups	75614.282	90	840.159		
Total	75875.160	93			
Sample Descriptives: SJR vs Number of citations					
SJR Rank	N	Mean	Std. Deviation	95% Confidence Interval for Mean	
				Lower Bound	Upper Bound
Q1	44	12.89	14.735	8.41	17.37
Q2	36	10.08	43.134	-4.51	24.68
Q3	10	9.30	10.822	1.56	17.04
Q4	4	7.50	5.916	-1.91	16.91
Total	94	11.20	28.563	5.35	17.05

IV.3. Conclusions and way forward

In our explorative analysis of HTA literature from the CEE and MENA regions, we observed that that the CEE countries have been progressing notably in the last 10 years while the MENA is still lagging far behind. This concludes that different health economic research contributions are needed for each region. Therefore, for the MENA region, we decided to dive deeper into the region's health economic evaluations, their types, quality, and active countries to identify the gaps in societal costs reporting. For the CEE region, we opted to narrow our source region into the V4 provided the relative concentration of HTA research output from the group, in addition to their similar political and economic states which should contribute to minimising interregional costs bias. In the following two chapters (V and VI) we proceed with the mapping of MENA health economic research to create a PL costs library for transferability facilitation.

V. CHAPTER: A SCOPING REVIEW OF HEALTH ECONOMIC RESEARCH FROM THE MENA REGION

This Chapter is based on the following published journal paper:

*Zrubka, Z., **Rashdan, O**., & Gulácsi, L. (2020). Health economic publications from the Middle East and North Africa Region: a scoping review of the volume and methods of research. Global Journal on Quality and Safety in Healthcare, 3(2), 44-54.*

This chapter aims to map the health economic literature from the MENA region summarising the scope of countries, diseases, technologies, methods, and overall bibliometric health economic performance. We also explore differences between high- and middle-income countries in research directions and methodological orientations. We also test our first hypotheses (i.e. H1: Given the superior financial capacity in high-income countries, we assume that their group will comprise the highest share of full economic evaluations from the MENA region).

V.1. Methods

Scoping review methodology was chosen as a regional literature analysis tool (Munn et al., 2018). Applicable PRISMA guidelines were followed in reporting our scoping review process (A. Liberati et al., 2009). MEDLINE (i.e. PubMed) was chosen as a source database given that it is the preferred database for medical research (De Leo, LeRouge, Ceriani, & Niederman, 2006).

V.1.1. Search criteria

Health economic publications were identified by devising a comprehensive keyword search criterion based on similar methodological studies (Decimoni et al., 2018; Glanville, Fleetwood, Yellowlees, Kaunelis, & Mensinkai, 2009). The concluded keywords used for the identification are in table 8.

Table 8. Keywords for health economic evaluations identification.

((outcome/s OR benefit/s) AND cost/s), cost saving, cost analysis, cost benefit analysis, cost analysis, economic evaluation, economic appraisal, cost effectiveness, cost utility, cost consequence, cost minimization, budget impact, decision model, HTA, health technology assessment, COI, cost of illness, cost of disease, CEA, CBA, CMA, CUA, DALY, QALY, quality adjusted life years, quality adjusted life year, disability-adjusted life years, disability-adjusted life year, ICER, cost effectiveness ratio, ACER, Markov model, quantitative evaluation, decision tree, health economic, discrete event simulation, program evaluation, decision making, expenditure, economic model, friction cost, contingent valuation, medical cost, medical costs, disease related cost, disease related costs, direct cost, direct costs, indirect cost, indirect costs, cost comparison, resource utilization, economic burden, pharmacoeconomic, pharmaco economic, cost effective.

For the MENA region, we chose to include countries speaking Arabic as an official language within the geographical space of the MENA. The following 17 countries were selected: Algeria, Bahrain, Egypt, Iraq, Jordan, Kuwait, Lebanon, Libya, Morocco, Oman, Qatar, Palestine, Saudi Arabia (KSA), Syria, Tunisia, the United Arab Emirates (UAE, including Dubai and Abu-Dhabi), and Yemen. The search was conducted on the 15th of Dec 2019 combining the health economic evaluation keywords with countries using Boolean "AND", with the search targeted for the "Title/Abstract" fields. Filters for English language and full-text publications were applied. The complete search code is showed in Appendix II.

V.1.2. Inclusion criteria

The initial inclusion/exclusion for the articles was implemented by first screening the results for eligibility from the title and abstract independently by two researchers (ZZ, OR). After joint selection, potentially eligible full-text articles were acquired, and their full text evaluated jointly in detail against all eligibility criteria detailed in this section. The entire process of screening citations, judgment about inclusion and exclusion was done parallel, and discrepancies cross-checked by the same two researchers (ZZ, OR). Any differences in the inclusion were each discussed and resolved by discussion until a joint agreement was reached.

Only Journal articles reporting original research on humans, involved the local population from the target MENA countries, was a full or partial health economic analysis were included. If the

intervention was compared with no action, it was considered as a comparison and was included (e.g. savings). Efficacy studies for medical health technologies reporting costs (ErC) were also included given that they can be an important source of health economic evidence (*Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011].* , 2011).

As for the exclusion criteria, although the English language, full text, and journal article filters were applied, we excluded all those which did not meet the criteria and still appeared in our search. We excluded speculative health economic studies (i.e. studies which claimed health economic research goals or conclusions in their title or abstract without providing sufficient methodological detail or description to support their claims). Studies that did not report cost comparisons or only reported costs as part of a questionnaire with no further calculation were excluded. Studies that did not compare two alternatives were excluded.

We also excluded conference proceedings, commentaries review papers, non-original research, studies that did not involve human subjects, or studies that were not economic evaluations or only had costs related questions as part of their survey with no further calculations. (e.g. resource use studies not reporting costs associated) were all excluded., although utilized to complement our search results, yet were excluded due to lack of originality. Pure methodological studies and studies conducted on non-native populations (e.g. non-native army, migrant populations, or pilgrims) were also excluded.

V.1.3. Tools and data Extraction

For data extraction and descriptives, a Microsoft Excel spreadsheet was prepared, Statistical analysis was conducted using Stata 14.2 statistical software (StataCorp, 2015). The first author's name, publication year, and the target country of the evaluation were recorded. We indicated whether the analysis comprised single or multiple MENA countries (multi-MENA) or if the analysis included other countries from other regions (multi-mixed). Corresponding author affiliation country and the funding source of the study were recorded into government, academic institution, non-governmental organisation (NGO), intergovernmental organisation (IGO), industry, mixed with industry involvement, or not available if no funding info were disclosed.

Using the criteria of the World Bank for country income groups (World Bank, 2019), countries were classified as per their income status. Bahrain, Kuwait, Oman, Qatar, KSA, and the UAE were classified as high-income countries, while the remaining were classified into middle-income or mixed-income countries if ranking fluctuated between income groups over the study period between low-, lower-middle- and upper-middle income categories. If the study included countries from different income levels, it was marked as mixed-income. We also reported the health technology under evaluation split into categories; medicine, vaccine, device (including diagnostics), procedure (e.g. cesarean section), and system (e.g. public health and screening programs, health insurance programs).

The type of economic evaluation was also recorded as per the criteria given by (M. Drummond, Schulper, & Claxton). We relied on the reported information and methods in the study to judge the methodological type of the study rather than what the authors claimed. Full economic evaluations were recorded if both health outcomes and costs were reported (i.e. cost-utility- (CUA), cost-effectiveness- (CEA), cost-benefit- (CBA), cost-minimisation- (CMA), and cost-consequence analyses (CCA)). In particular, and due to the unstandardized nature of some of the studies, programs reporting multiple outcomes in complex tubular format were categorised as CCA, and studies reporting equality of outcomes for interventions were categorised as CMA. For partial economic evaluations, we recorded Budget impact analysis (BIA), Cost-volume-profit analysis (CVP), and cost comparisons (CoC) as well as efficacy studies reporting costs (ErC).

The studies' perspective (i.e. society, health system, health institution (e.g. hospital), patient or other (e.g. third-party payer)) was recorded. we also captured the study type between trial and model-based (primary research with model inputs was considered as trial-based). The costing year was also recorded for each study. Whenever the costing year was not specified, or the study was undertaken over multiple years, the publication year or the final study year was reported. We searched and selected the journal subject area and the Scimago journal rank (SJR) in the publication year. If articles were published before 1999 (before SJR) or unindexed, they were

categorised as not available, while studies published in 2019, received the journal rank of 2018. We finally evaluate the quality of the economic evaluations using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) (Husereau et al., 2013). Fisher's exact test was used to test our first hypothesis (H1).

V.2. Results

Our search order resulted in 2017 hits, went down to 1646 after applying English language and full-text filters. Screening by title/abstract resulted in 219 articles eligible for full-text assessment. From those we excluded 114 articles due to the following reasons: not original research on humans (n=13), the full text was not English (n=2), not the local population was studied (n=7), no health technology was evaluated (n=9), the study was not a health economic evaluation reporting costs (n=6), no alternative technologies were compared (n=61), (n=15) speculative studies and (n=1) duplicate study. The final number of articles eligible for our analysis was 105 articles. Figure 7 shows the Prisma diagram of the MENA literature review from identification, through screening, exclusion/inclusion to eligibility, and inclusion.

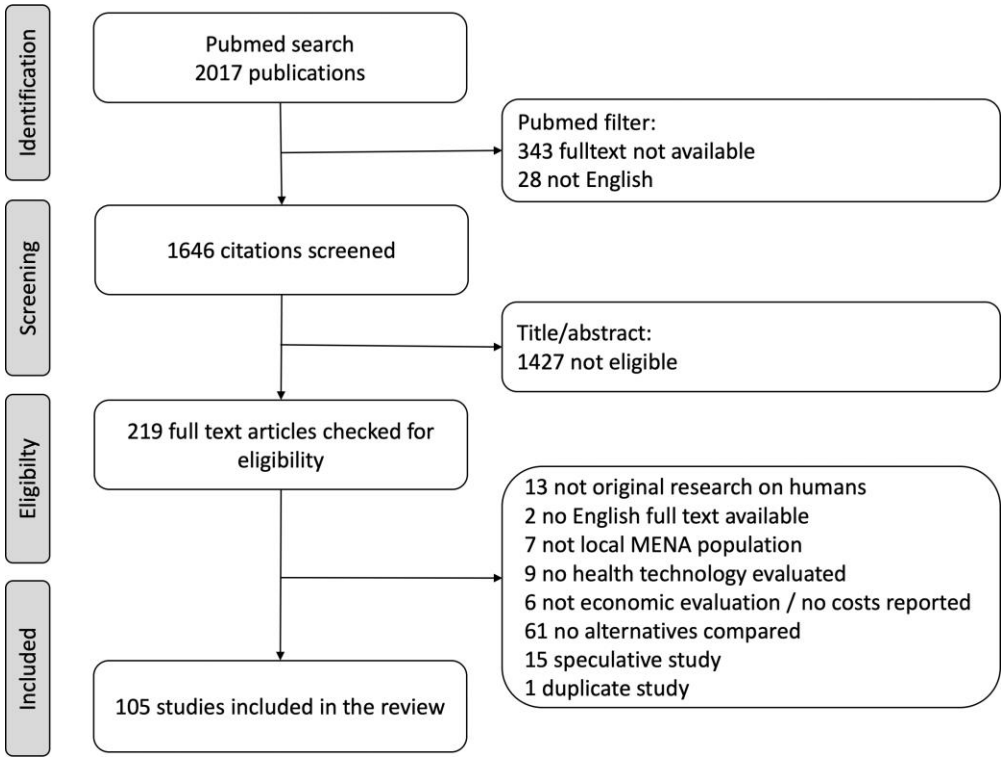


Figure 7. Prisma diagram. identification, screening, eligibility, inclusion. *Source: (Zrubka, Rashdan, & Gulácsi, 2020)*

V.2.1. Publication's timeframe and geographical scope

Figure 8 shows a bar chart for the distribution of MENA health economic publications by year. The first study was published in 1989 and the literature volume has considerably increased in the last 5 years (n=60, 57.1%), before which the number of publications was saprobic (n= 45, 42.9%) over the 35 years previous to 2015. Most of the studies were specific for a single country (n=91; 62.8%), 3 (2.9%) studies involved multiple countries from MENA, and 13 (12.4%) studies were international involving countries from inside of MENA.

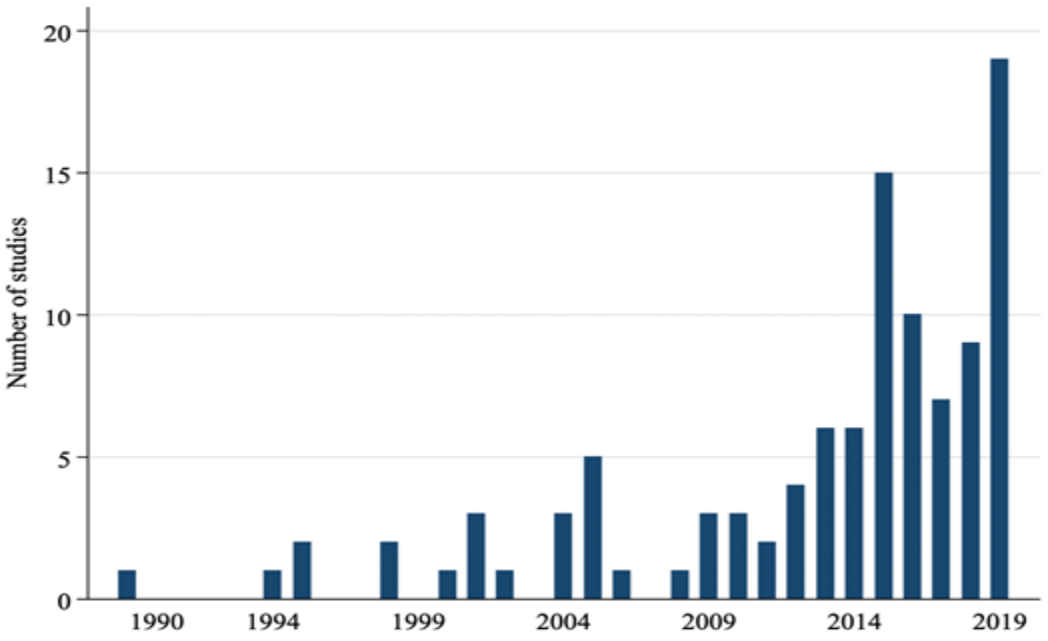


Figure 8. Number of studies by publication year (n = 105). *Source: (Zrubka et al., 2020)*

Figure 9 shows a gradient map of the number of studies per country. We have found 145 country-specific health economic results from our 105 studies; middle-income countries comprised most of the results (n = 91; 62.8%). Most studies reported results from Egypt (n = 32; 30.5%), KSA (n = 29; 27.6%), and Jordan (n = 10; 9.5%). No single country (designated) studies were found reporting evidence from Yemen and Lebanon.

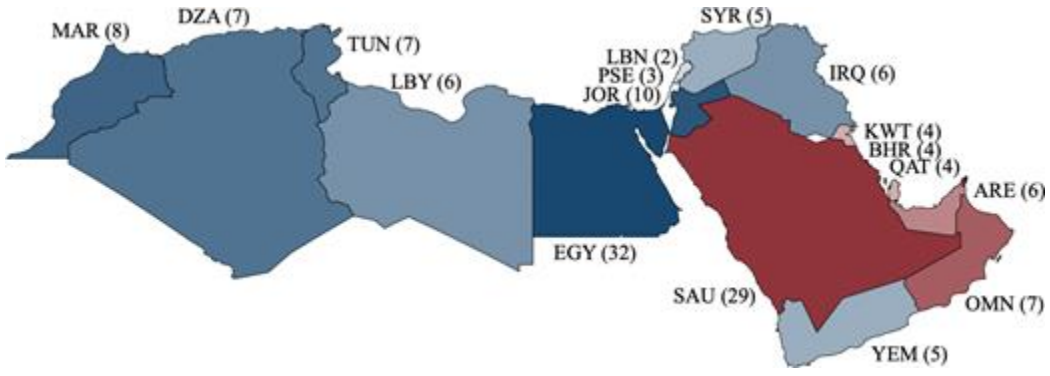


Figure 9. Gradient MENA map presenting the number of analyses per country. *Source: (Zrubka et al., 2020)*

V.2.2. Disease areas

Disease areas investigated within the region belong to all ICD-10 chapters except for chapter XII (diseases of the skin and subcutaneous tissue) and the disease area was not specified in 11 studies (Figure 10), The most investigated indications in terms of quantity were hepatitis C (n = 7; 6.7%), rotavirus enteritis (n = 5; 4.8%), renal failure (n = 5; 4.8%), diabetes mellitus (n = 4; 3.8%), cervical cancer (n = 3; 2.9%), and caesarean section (n = 3; 2.9%). Fisher's exact test results for disease groups difference between country income groups was significant (Fischer's exact test, p = 0.004); in high-income countries, the most frequently investigated diseases were from ICD-10 chapters chapter XI, digestive diseases (n = 6; 15.4%), chapter I, infectious diseases (n = 6; 15.4%), and chapter IX, circulatory diseases (n = 5; 12.8%). From middle income countries; chapter I, infectious diseases (n = 20; 37.7%), chapter II, neoplasms (n = 5; 9.4%), chapter IV, genitourinary diseases (n = 4; 7.6%), and chapter XIX, injuries/external causes (n = 4; 7.6%). While in mixed income countries; chapter I, infectious diseases (n = 3; 23.1%), chapter IV, endocrine diseases (n = 3; 23.1%), and chapter IX, circulatory diseases (n = 3; 23.1%) were most frequent.

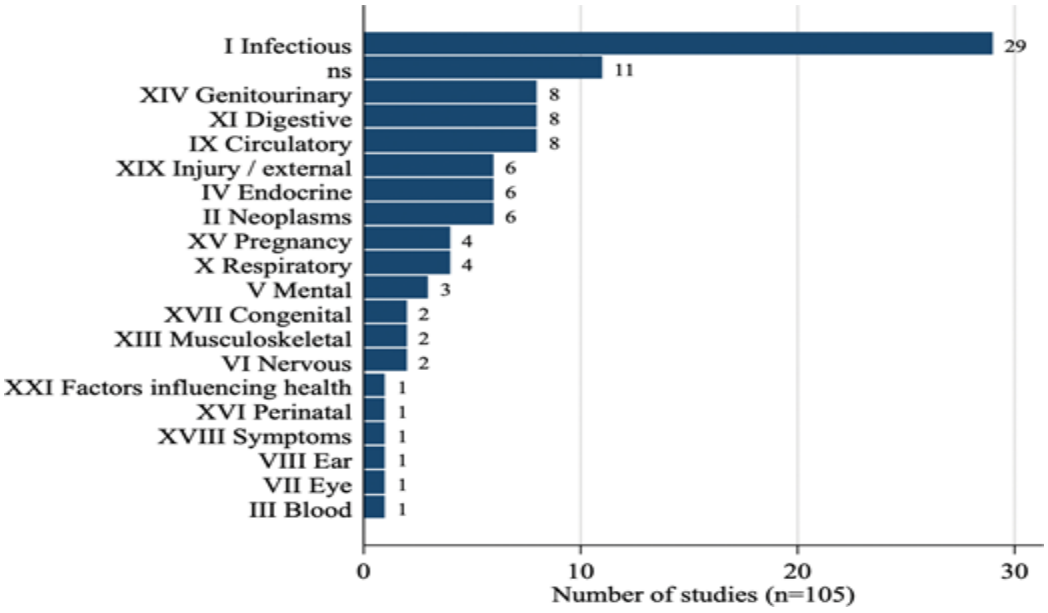


Figure 10. Number of studies by ICD-10 disease area (n = 105).

V.2.3. Health economic evaluation methods and technologies

Figure 11 illustrates the methodological details of the studies. Over half of the studies (n=52; 49.5%) were full economic evaluations. The applied method was CUA, CEA, CCA, CMA and CBA in 29.5% (n=31), 14.3% (n=15), 3.8% (n=4), 1.0% (n=1) and 1.0% (n=1) of studies, respectively. On the other hand, 29 (27.6%) partial economic evaluations involving 10 (9.5%) BIA studies and 19 (18.1%) cost-comparisons were found. ErC studies comprised 22 (21.0%) and 3 (2.9%) papers were of other methods (e.g. CVP analysis).

Middle-income countries comprised the largest proportion of full economic evaluations (n=29; 54.7%) compared to (n=13; 33.3%) in high-income countries. The use of the main evaluation methods (i.e. full, partial, and other evaluations and efficacy studies reporting costs) was significantly different between country income groups (Fischer's exact test, p = 0.04). The proportion of full economic evaluations (n = 29; 54.7%) was greater in middle-income compared to high-income countries (n = 13; 33.3%), hence we reject our first hypothesis (*H1*) that provided the high financial capacity, we would expect high-income countries to comprise the highest proportion of full economic evaluations.

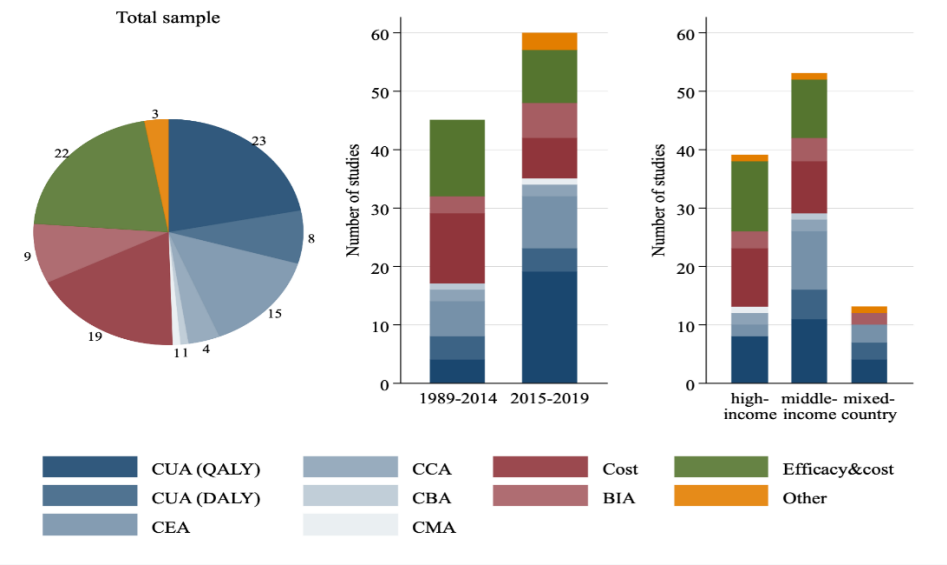


Figure 11. Number of studies by type of economic evaluation (n = 105). Source: (Zrubka et al., 2020)

V.2.4. Health technologies, perspective, funding, and study types

In terms of the type of health technologies evaluated in the region, studies mainly investigated systems (n=44; 41.9%), followed by medicines (n=31; 29.5%), vaccines (n=12; 11.4%), devices (n=10; 9.5%) and lastly procedures (n=8; 7.6%). While in terms of perspective, over half of the study adopted a health system perspective (n=55; 52.4%), followed by healthcare institution (n=28; 26.7%), societal (n=9; 8.6%), patient (n=8; 7.6%) and other perspectives (n=5; 5%) such as third-party payer perspective.

Among the 9 studies adopting a societal perspective, n=5 were QALY-based CUA (4.8%), n=2 were DALY-based CUA (1.9%) and 2 were CEA (1.9%) studies. In terms of funding; industry, government, IGO, academic institution, NGO comprised 17.1% (n=18), 12.4% (n=13), 5.7% (n=6), 4.8% (n=5), 4.8% (n=5) respectively, while funding was not indicated in 31.4% (n=33) and was stated as none in 22.9% (n=24) of the articles. The studies were mainly trial based 56.2% (n=59), followed by model-based 41.9% (n=44) and econometric in 1.9% (n=2) of the total sample.

V.2.5. SJRs

SJR was Q1 in 49 (46.7%) papers, Q2 in 25 (23.8%), Q3 in 20 (19.1%) and Q4 in 1 (1.0%) and was not available in 10 (9.5%) publications. The proportion of Q1 publications was as high as 92.3% (n=12) in mixed-income country studies, while it was 43.4% in studies from middle-income and 35.9% (n=14) in studies from high-income countries. Only five studies reported adherence to the CHEERS list guidelines. Sensitivity analysis was performed in 47 (44.8%) studies; one-way was applied in 38 (36.2%) studies, probabilistic in 14 (13.3%), and multiway in 12 studies (11.4%). Figure 12 illustrates SJR for our results, stratified by type of evaluation and income level.

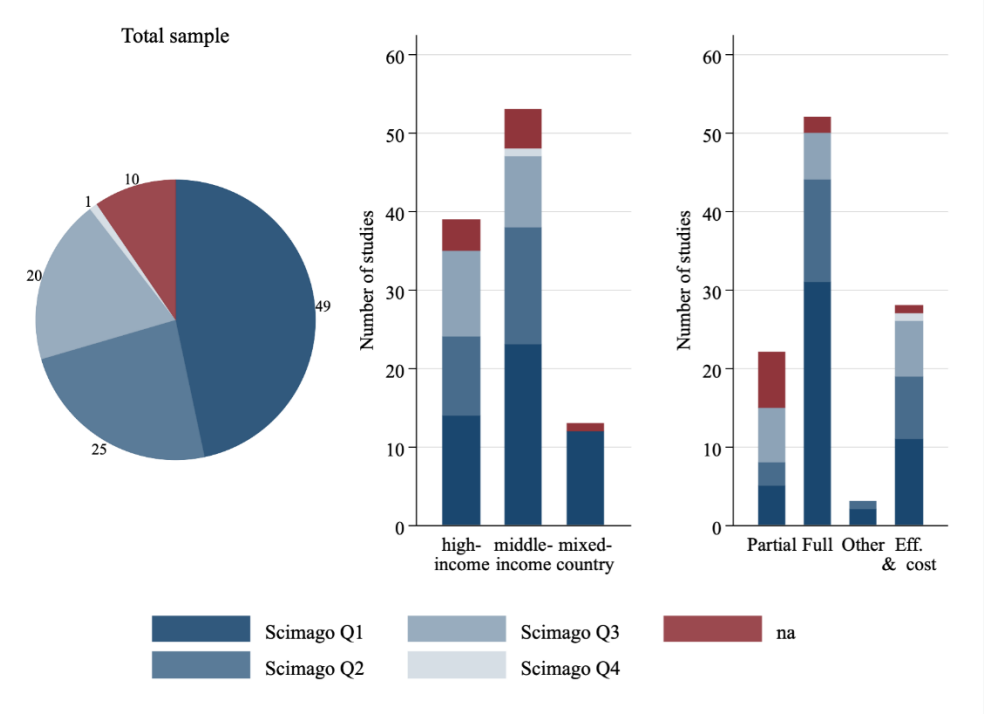


Figure 12. Number of comparative health economic studies stratified by SJR, type of evaluation, and country income level (n=105). *Source: (Zrubka et al., 2020)*

V.3. Discussion

To the publication date of this chapter, our scoping review is the largest account of comparative health economic evaluations for the MENA region. The 105 identified evaluations, their targeted countries, diseases, technologies, and methods in addition to their bibliometric properties were analysed. Globally, the MENA region provided 2% of the global publication output of full health economic evaluations published between January 2012 and May 2014 (Pitt, Goodman, & Hanson, 2016). However, significant growth in the publications started emerging after 2014 given that more than half of the evaluations were published in the past 5-6 years. This strongly suggests that the field interest is recently increasing in the region.

The countries scientific output of health economic publications followed a similar proportion of overall scientific activity as reported by UNESCO (Zoubi, Mohamed-Nour, El-Kharraz, & Hassan, 2015); led by KSA and Egypt and followed by Tunisia, Algeria, and Morocco, except for Jordan, which ranked 8th in the UNESCO report, but third in ours after Egypt. Including multi-country

studies, 145 country-specific results were identified, of which the majority were from middle-income countries rather than high-income countries. Almost half of the studies were full economic evaluations in which the health system was the predominant perspective while third-party payer perspective was among the lowest adopted perspectives. Although the number of QALY-based CUA studies increased rapidly over the last 5 years, yet the lack of local value-sets for major generic health-related quality of life (HRQoL) measurement instruments (i.e. EQ-5D, SF-6D, and HUI) (EuroQoL Group; Horsman, 2012) may have contributed to slowing health economic research in the region.

We noticed that infectious disease was the top investigated disease group in the region. Differences in health economic research orientation were significant among income groups as the majority of studies on infectious diseases originated from middle-income countries while the majority of studies on digestive, respiratory, and circulatory diseases focused on high-income countries. Public health priorities in the region as reported by the (Institute for Health Metrics and Evaluation; Human Development Network; The World Bank, 2003) concluded almost two decades ago that musculoskeletal and mental disease were among the top five leading causes of disability in the region, yet our results show that those two disease groups were respectively at the 12^{th} and 10^{th} place among the overall studied disease areas in the region suggesting that health economic evaluations in the region only partially followed regional public health priorities, and was more likely reliant on data availability or current funding rather than targeted long term plan.

Future research should follow the regional needs rather than the sporadic dissemination of scarce, local expertise time. Out of diverging priorities from recommendations, the importance of assessing NCDs' societal burden for the region can be of significant value in light of such specific scarcity in the region's literature. For that reason, a more comprehensive search is needed to gather NCD PL costs utilising to facilitate transferability efforts. Provided the limited availability of indirect cost estimates, we proceed with creating a regional catalogue for PL costs to aid in future transferability efforts as will be demonstrated in chapter VIII.

Our review has several limitations; in addition to the suboptimal sensitivity of our search filter, other sources of health economic publications, such as conferences and grey literature (CADTH, 2019) were not searched in our study. moreover, we excluded articles where the full text was not available in English language. Consequently, important publications may have been missed given the strongly varying importance of French or Arabic language over the region (Ballais et al., 2018) which was also demonstrated in our third chapter. However, due to the strong regional political direction towards improving international scientific impact over the last 10 years (Zoubi et al., 2015), focusing on English publications can provide a good idea of the overall health economic research activity in the MENA.

VI. CHAPTER: A SYSTEMATIC REVIEW OF PRODUCTIVITY LOSS (PL) COSTS IN THE MENA: TOWARDS A REGIONAL PL CATALOUGE

This chapter is based on the published poster presentation and abstract in ISPOR Europe 2020, November.

Rashdan, O., Brodszky, V., Péntek, M., Gulácsi, L., & Zrubka, Z. (2020). PNS32 Towards a Healthcare Cost Catalogue for Middle EAST and North Africa: A Systematic Review of Productivity Loss Costs Reported in Health Economic Publications between 1989-2019. Value in Health, 23, S649.

In the previous chapter, our review encompassed the largest number of health economic studies from the MENA region (n=105) compared to other regional high-quality reviews; S. A. Al-Aqeel (2012); (I. Eljilany, F. El-Dahiyat, L. E. Curley, & Z. U. Babar, 2018; Farid, Elmahdawy, & Baines, 2019). In contrast to our inclusion of evaluations assessing the value of alternatives, the other reviews included also those studies evaluating a single intervention. Those three reviews gave a total of 78 articles, out of which 51 were not included in our previous study, and 27 studies overlapped between us and the three reviews. On the other hand, 23 extra studies were included in our review, which were potentially eligible, yet not included in previous regional reviews.

The aim of this chapter is the comprehensive identification of all PL reporting health economic evaluations from the MENA region, and the establishment of a MENA PL costs library facilitating future PL regional research and transferability. We also will be testing our second hypothesis (*H2*) where we expect a significant association between country income groups and the choice of investigated ICD-10 disease chapters as we assume that high income countries are more involved in PL costs assessment.

VI.1. methods

The search criteria were adopted from (Zrubka et al., 2020). The search was performed on the 15th of December 2019 with English language and Full-text filters applied. Resulting articles

Title/abstract were screened by two authors in parallel (ZZ, OR), judgments were cross-checked, and any discrepancy was resolved after discussion. Articles from similar regional reviews (S. A. Al-Aqeel, 2012; I. Eljilany, F. El-Dahiyat, L. E. Curley, & Z.-U.-D. Babar, 2018; Farid et al., 2019) were reviewed, and any missing article from our results was added, provided meeting the inclusion criteria laid in the next section.

VI.1.1. Inclusion criteria

We included journal articles reporting original research on humans, involved the local population from the target MENA countries, and reported PL costs using any evaluation method were included matching with our previous inclusion criteria in chapter IV. In contrast to our previous chapter's criteria, we opted to include speculative studies (as long as their results were justified) as well as studies with or without comparators, as long as they reported PL.

Conference proceedings, commentaries, non-original research, studies that did not involve human subjects, or studies that were not economic evaluations or only had costs-related questions as part of their survey with no further calculations. (e.g. resource use studies not reporting costs associated) were all excluded. Pure methodological studies and studies conducted on non-native populations (e.g. non-native army, migrant populations, or pilgrims) were also excluded. Review papers, although utilized to complement our search results, yet were excluded due to lack of originality.

VI.1.2. Data extraction and variables

For data extraction, a Microsoft Excel spreadsheet was developed according to a predefined criterion. For each article, the first author, the publication date, and the target country of the analysed population were extracted. We indicated whether the analysis included multiple MENA countries or countries from other regions. Using the criteria of the World Bank (World Bank, 2019), countries were classified as per their income status. Bahrain, Kuwait, Oman, Qatar, KSA, and the UAE were classified as high-income countries, while the remaining eleven countries were classified into middle-income countries (i.e. Algeria, Egypt, Iraq, Jordan, Lebanon, Libya, Morocco, Qatar, Palestine, Syria, Tunisia, and Yemen) form simplification and due to fluctuations

between income groups over the study period in addition to their comparable local purchasing power. We also recorded for each evaluation the corresponding ICD-10 disease chapter disease name and code (i.e. 5th edition). For screening activities, we reported the disease it is intended for, not the activity itself (e.g. depression screening→depression).

The type of evaluation was recorded in the same manner we reported in our previous review in chapter IV. In short, full economic evaluations comprised; cost-utility- (CUA), cost-effectiveness- (CEA), cost-benefit- (CBA), cost-minimisation (CMA), and cost-consequence analyses (CCA). While for partial economic evaluations, we recorded Budget impact analysis (BIA), Cost-volume-profit analysis (CVP), and cost comparisons (CoC) as well as efficacy studies reporting costs (ErC). We also identified the studies' data sources between primary, secondary, or model-based. Whenever the costing year was not specified, or the study happened over multiple years, the publication year or the first study year was reported.

We finally extracted all PL cost items reported in our included articles. Due to the unstandardized methodological cost reporting in the region's publications; we relied on (M. F. Drummond et al., 2015) criteria for health economic evaluation in our judgment with each cost item to decide the appropriate cost category rather than what the author's nomenclature suggested (e.g. some researchers refer to administrative costs as indirect costs, while in fact, they go under the direct costs category). Each cost item was recorded along with its denominator, cost description, PL cost category (total, Indirect), cost Type (absenteeism/morbidity, presenteeism, or mortality), cost currency, and cost year. Total costs were reported if they had any component of PL within.

VI.1.3. Analysis tools

The analysis was performed in Excel 365 utilizing pivot tables and charts to visualise the data and "Tableau" software was used to map the cost items as per their corresponding ICD-10 chapters and diseases. To test, SPSS was used to test our second hypothesis (H2) regarding the association of income level with the investigated diseases chapter. We used fisher's exact test for 2x2 tables while chi-squared test was used for larger tables. Likelihood ratio was reported instead of chi-

square test when the minimum expected cell count assumption was violated. Cramer V statistic was reported for significant categorical associations to indicate association level.

VI.2. Results

The search resulted in 1675 hits which were decreased to 248 studies after Title/abstract screening. From those, n=63 studies were excluded (i.e. 13 non-original research, 23 had costs from before 1995, 18 reported no costs, 7 were for a non-local population, and for 2 articles no full text was found). The remaining 185 articles were thoroughly screened for indirect costs inclusion to finally include 23 eligible articles (i.e. contain productivity loss/indirect costs involving local country populations for at least one of the selected seventeen MENA countries). Figure 13 below shows the Prisma flowchart of the review process.

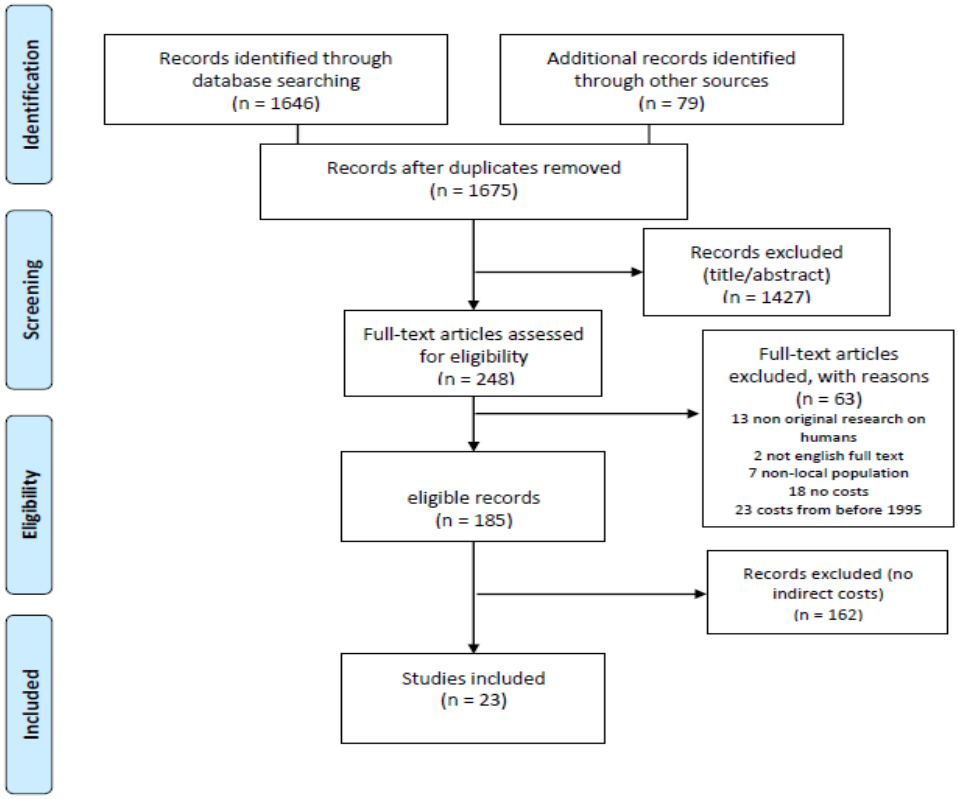


Figure 13. Prisma flowchart for MENA PL costs identification.

VI.2.1.PL Studies characteristics

The first health economic study reporting PL costs from the MENA region was published in 2001 and over the next 10 years, only 5 more articles were published. Most of the studies were published after 2011 (n=17, 74%), while the year 2015 had the highest number of publications (n=5, 22%). Figure 14 splits the publications by country in a pie chart. All identified studies focused on a single country and reported country-specific PL costs. KSA had the highest share of regional publications (n=6, 26%), followed by Egypt (n=4, 17%), while the rest (i.e. Yemen, Tunisia, Libya, Jordan, Qatar, Palestine, Bahrain, Oman, and Morocco) published two or one study only, representing 57% of the region's publications. Over 62% (n=14) of the studies concerned the middle-income countries group while nearly 38% (n=9) of the studies concerned upper-income countries, while we have not found any studies from Algeria, Iraq, Syria, UAE, Sudan, or Lebanon.

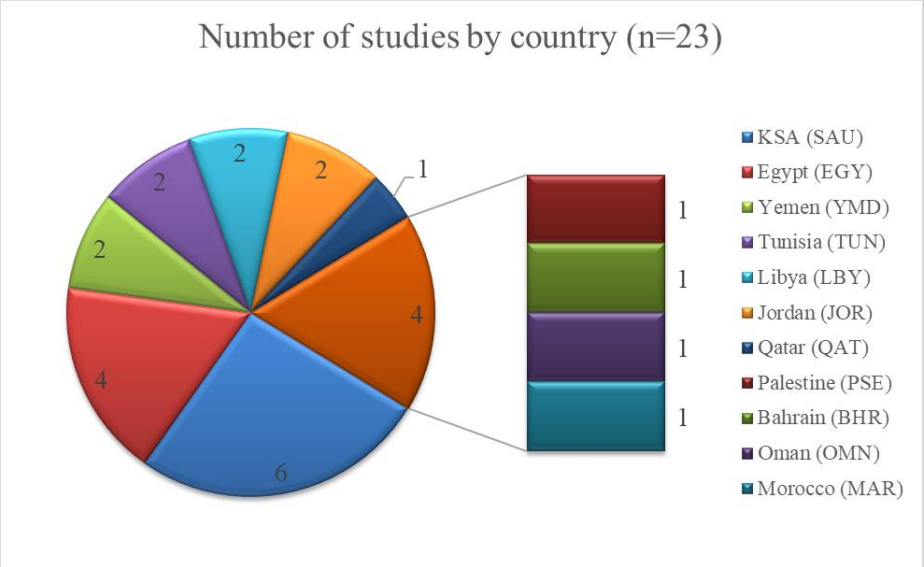
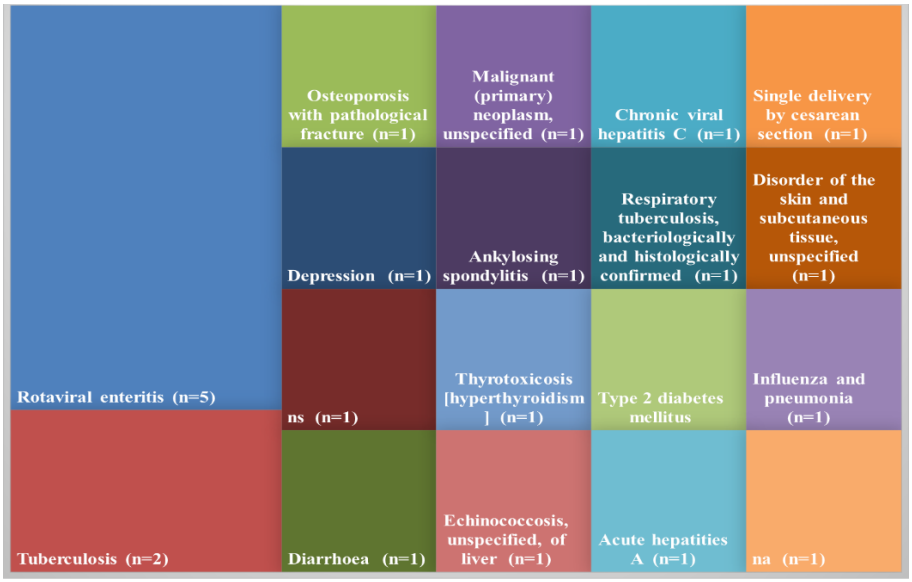


Figure 14. Number of MENA PL reporting publications by country.

Figure 15 shows a hierarchal map of the diseases investigated in the health economic evaluations in the MENA region. Overall, sixteen diseases were investigated belonging to nine ICD-10 chapters with chapter I (Certain infectious and parasitic diseases) encompassing over half of the studies (n=12, 52%). Two diseases were of major regional concern, Rotavirus enteritis (n=5, 22%) and Tuberculosis (n=2, 9%). All other investigated diseases warranted only one study each, which

signifies the necessity of further regional estimations. Regarding the health economic evaluation methods employed, the studies used nine different health economic evaluation methods, (n=7, 30%) were COI, (n=4, 17%) CEA, (n=3, 13%) BoD, while CBA, CUA and ErC were each used twice (n=2, 9%) and CVP, CMA and CoC were each used once (n=1, 4%). As a data source, most of the studies were primary research (n=13, 57%) while (n=6, 23%) relied on a secondary data source and (n=4, 13%) were model-based. Included articles' descriptive results are tabulated and mapped as per their ICD-10 chapters and evaluation type in Appendix III.



* na: not applicable **ns: no specific disease

Figure 15. Hierarchal map of the number of MENA PL reporting studies as per their corresponding ICD-10 disease name.

VI.2.2. PL cost items characterisation

From our 23 articles, we extracted 95 PL cost items in total. Table 9 shows our frequency tables resulting from clustering our extracted cost items. costing year frequencies are showing 2003 and 2012 with the highest count of cost items reported over the years (n=22, n=18, respectively), a decrease in reported PL items can be noticed in the last 5 years. United States dollar (USD) currency was the most used for reporting cost items (n=55), followed by SAR (n=31) while n=8

items were reported in Tunisian dinar, Jordanian dinar, and Purchasing power parity (PPP). Regarding the type of evaluations those items are reported in, CUA studies reported n=18 items, COI n=25, CEA n=13, CBA=22, while n= 27 were distributed among other methods.

Most PL costs (n=47) were reported for absenteeism and total cost including PL (n=37), then mortality cost (n=4), caregiver PL (n=4) and presenteeism PL (n=3). Middle-income group countries comprised the highest share of cost items (n=52), although slightly comparable to high-income countries group (n=43). Most of the cost items were reported from primary studies (n=45), followed by secondary studies (n=34) and (n=16) were from model-based studies. When classifying per disease category, most PL costs were reported for ICD-10 chapter I (Certain infectious and parasitic diseases n=51) followed by chapter X (Diseases of the respiratory system, n=21), (n= 21) were distributed among 6 chapters, and the remaining (n=2) cost items were not for a specific disease (e.g. catheterisation services). It is worth noting much less concentration was given to the region's health priorities as musculoskeletal diseases (n=7), and mental disorders (n= 6) were underrepresented.

A significant association ($p<0.000$) was found between country income groups and the investigated ICD-10 disease chapters, with high association level (Cramer's V=0.808) as middle-income countries reported 84.3% of PL costs for ICD-10 chapter I (Certain infectious disease and parasitic diseases). Hence, we accept our second hypothesis (H2) that there is a significant association between the investigated diseases and the country income group. Income groups also had a significantly high association with the study type ($p<0.000$, Cramer's V 0.645) as middle-income countries comprised 77.8% of PL cost items reported in primary studies and 81.3% of modelling studies, while for high-income countries, costs were mainly attained through a secondary study (88.2%). No significant association was found between income groups and PL item type (P=0.068) neither between the investigated ICD-10 chapter and reported PL item type (0.059). Detailed association results are presented in appendix III.

Table 9. Frequency tables for MENA PL cost items (n=95)

PL cost items frequencies by PL items count			
Cost year		**Currency**	
2016	3	USD	55
2015	1	TND	5
2014	2	SAR	31
2013	9	PPP$	2
2012	18	JOD	1
2011	2	BHD	1
2010	9	Total	95
2009	9	**PL cost type**	
2006	5	total cost including PL	37
2005	2	presenteeism PL	3
2003	22	mortality PL	4
2000	5	caregiver PL	4
1999	8	absenteeism	47
Total	95	Total	95
Country		**Evaluation Method**	
Yemen (YMD)	10	ErC	7
Tunisia (TUN)	9	CVP	1
Syria (SYR)	2	CUA	18
Qatar (QAT)	2	COI	25
Palestine (PSE)	1	CoC	2
Oman (OMN)	7	CMA	1
Morocco (MAR)	2	CEA	13
Libya (LBY)	14	CBA	22
KSA (SAU)	33	BoD	6
Jordan (JOR)	4	Total	95
Egypt (EGY)	10	**Study Type**	
Bahrain (BHR)	1	secondary study	34
Total	95	primary study	45
Income group		model	16
Middle income	52	Total	95
High income	43		
Total	95		
ICD-Chapters			
XV Pregnancy, childbirth and the puerperium	2	ns	2
XIII Diseases of the musculoskeletal system and connective tissue	7	IV Endocrine, nutritional and metabolic diseases	2
XII Diseases of the skin and subcutaneous tissue	2	II Neoplasms	2
X Diseases of the respiratory system	21	I Certain infectious and parasitic diseases	51
V Mental and behavioural disorders	6	Total	95

*ns: not specified.

VI.3. Discussion

This chapter presents the largest pooling of disease PL costs from the MENA region. We extracted, categorised, and mapped out the regions' PL costs to facilitate future field research, and boost transferability efforts in the region. Our extracted costs mostly came from partial economic evaluations (61%), with COI and BoD comprising over 43% of those studies. On the other hand, full health economic evaluation comprised 39% of our sample, with CEA and CUA studies reporting about a quarter of the total reported PL costs (26%). Egypt contributed to the majority of the full economic evaluations in the MENA region with (n=3) studies, followed by KSA and Jordan with each contributing with (n=2) studies. While KSA had the highest share of partial economic evaluations with (n=4) evaluations. Research output in the field followed more or less UNESCO's ranking with minor differences such as KSA preceding Egypt in rank (Unesco, 2015).

In light of reported PL costs distribution, almost half of the reported PL costs were for absenteeism (49.5%, n=51), and only (11.6%, n=11) PL cost items were reported for presenteeism, mortality, and caregivers combined. COI studies had the highest count of reported PL costs (26%). Infectious disease comprised the majority of the region's extracted PL costs (54%) with middle-income countries contributing to 84.3% of the total reported infectious disease PL costs. Diseases of the respiratory system had the second-largest share of reported PL costs with 22% of total reported PL cost items. This follows epidemiologists' recommendations for regional disease priorities (Abdallah, Taktak, Chtourou, Mahouachi, & Kheder, 2011; Ahmed, Robinson, & Mortimer, 2017).

Among the investigated NCDs, diseases of the musculoskeletal system chapter (Brämer, 1988) although were third in line after infectious and respiratory diseases in terms of PL costs count, yet only one study reported indirect costs for musculoskeletal disease from the MENA (Younes et al., 2010). In such mobility limiting diseases, the social impact is undeniable on both the patient and the caregiver. Such costs are often ignored due to lack of local evidence or due to limited financial capacity to design accommodating programs (King et al., 2018). Scarce efforts have been shown

in the region to address musculoskeletal disease and its societal cost. Our review has concluded sufficient PL costs from the musculoskeletal disease chapter to test for our transferability hypotheses. But first, we steer our direction towards the identification of local significant demographic, health status, and utility factors impacting PL costs in an attempt to develop an understanding of PL determinants on a micro- and macroeconomic level, to aid in our regional PL costs transferability adjustments.

Among the limitations to this work was the exclusion of other sources of health economic research such as conferences and grey literature, as these could be a valuable source of information. Moreover, we excluded articles where the full text was not available in English language. Consequently, important publications may have been missed provided Arabic and French languages from the region. Finally, the PICO framework for health economic evaluations was not completely reported provided the diverse types of health economic evaluations and the sub-optimal clarity of many studies creating substantial gaps among the studies.

VII. CHAPTER: PRODUCTIVITY LOSS FACTORS IN NCD PATIENTS: A POOLED ECONOMIC ANALYSIS

This chapter is based on the published journal paper:

***Rashdan, O**., & Brodszky, V. (2020). Productivity Loss in Patients With Chronic Diseases: A Pooled Economic Analysis of Hungarian Cost-of-Illness Studies. Value in Health Regional Issues, 22, 75-82.*

This chapter aims to pool and rank the productivity loss (PL) costs for eleven NCDs and identify significant local PL drivers (demographics, health status, resource use). We also set contrast for PL determinants between working and retired populations. In the following sections, we describe the methods, lay out the results, and discuss our findings in light of PL costs generalisability. Here within, we test our third hypothesis (H3) in which we assume that both health status and educational level have a significant impact on musculoskeletal disease PL costs.

VII.1. Methods

VII.1.1. Data sources and measurement tools

This work started by collecting and compiling the available raw PL data of eleven NCD evaluations from Hungary. Studies were non-interventional, cross-sectional, retrospective, COI studies, conducted in different medical centres in Hungary between the years 2003-2015. Our analysis encompassed the following eleven chronic diseases: psoriatic arthritis (Brodszky et al., 2009), benign prostatic hyperplasia (BPH) (Rencz et al., 2015), dementia (Érsek et al., 2010), diabetes (Jermendy et al., 2017), epilepsy (Pentek et al., 2013), multiple sclerosis (Pentek et al., 2012), Parkinson's disease (Tamás et al., 2014), psoriasis (Balogh et al., 2014), rheumatoid arthritis (Márta Péntek et al., 2007), schizophrenia (M Péntek et al., 2012) and systemic sclerosis (Minier et al., 2010). Patient-level raw data on demographics, health-related quality of life, resource use, and productivity loss for each disease were collected directly from the patients (or their caregivers) by the department of health economics at Corvinus University of Budapest and were later combined for this work. In all studies, EQ-5D-3L scores were measured using the

validated Hungarian version. EQ-5D-3L is the health status tool of choice recommended by many health technology assessment organizations (Mukuria et al., 2017). Local ethical approvals were obtained if the study was conducted in a single institution, while national ethical approval was acquired in case the study was conducted in multiple medical centres within the country. All patients signed an informed consent form about the use of their data. Specific information on each included COI study, such as costing year, gross wage, productivity loss measurement method (WPAI or open question), as well as the adopted costing approach (i.e. HCA/FCA), were directly extracted from their corresponding publications. We also extracted the publishing language (English/Hungarian), costing year, the gross national wage in that costing year as reported by the authors.

VII.1.2. Costing

All included COI calculations were performed employing a societal perspective (including direct and indirect costs) and applied similar methods to measure time off work and resource use. Patients were asked about sick leave days and their employment current status, including whether they were entitled to disability pension due to the disease or not. Indirect costs for each disease were calculated separately by multiplying the number of lost productive hours with the national gross wage in the corresponding study year. Adjusted indirect costs were then calculated for each disease to reflect the value in 2018-euro rates. We did not readjust for 2020-euro values since the macroeconomic data for the year 2020 was not published at the time of conduction in addition that the currency inflation was negligible during those two years (i.e. 1.4%).

Indirect costs adjustment was done by dividing the average gross wage for 2018, by the average gross wage for the study year, to obtain a specific conversion factor (i.e. gross wage rate) which was then multiplied with the corresponding disease indirect cost to obtain the adjusted PL cost for all investigated NCDs in unified 2018 euro rates. Moreover, indirect costs were expressed as a percentage of GDP per capita for the year 2018 (indirect costs/GDP/capita) by dividing each disease's adjusted indirect cost by the 2018 national GDP/capita in Hungary. The average national gross wage in Hungary for the year 2018 was acquired from the Hungarian central statistical office

website (Hungarian Central Statistical Office, 2018b) which amounted to HUF 329,900 = 1034.5 Euros (318.9 HUF = 1 Euro). Similarly, the 2018 Hungarian GDP/capita (13,686 Euros) was also obtained from the same source (i.e. Hungarian central statistical office website) emphasising costing consistency (Hungarian Central Statistical Office, 2018a).

VII.1.3. Statistical methods and study variables

SPSS 23 software (SPSS Inc., Chicago, IL, USA) was used for data management and statistical analysis. The attributes investigated in our analysis fall into three categories; PL variables (i.e. number of missed working hours and indirect costs), demographic variables (i.e. age, gender, and educational level), resource use variables (i.e. number of GP visits, number of outpatient visits, number of hospital admissions and informal care use) and health status variables (disease duration, EQ-5D-3L index). Disease dummy variables for each disease were also created to address the association (if any) between a specific disease and PL. Table 10 shows the utilised variables and their type.

Table 10. Variables utilized in our Hungarian NCD PL analysis along with their type.

Variable name	Variable type
Patient ID	nominal
Disease type	nominal
Age	scale
Gender	nominal
Education	ordinal
number of GP visits	scale
number of outpatient visits	scale
number of hospital admissions	scale
informal care	nominal
disease duration	scale
EQ-5D-3L index	scale
Indirect cost	scale
11 Disease-specific dummy variables	nominal

We investigate the gender (male/female), educational level (university degree/no university degree) and informal care (received/did not receive) group mean differences of lost productive hours using statistical tests of means equality. ANOVA analysis was used to compare disease group means of lost productive hours for each subgroup. On the other hand, Spearman's rho was

employed to identify significant correlations between the scale variables (resource use, health status (i.e. EQ-5D-3L score), and age with PL. To test our hypothesis (H3), we used both correlation and analysis of means methods.

To build our PL predictive models, curve estimation tool in SPSS was first used to confirm the adequacy of linear regression to explain our variables. Weighted linear regression (WLS) was then carried on to account for the different NCD sample sizes. The weighting variable was specifically devised to account for the differences in the sample size between diseases by dividing "100" by the number of patients in each disease group to obtain a disease-specific value. The resulting weight value for each disease was then incorporated into our models as the regression weighting variable, subsidising the effect of sample size in our models.

Due to some missing information in our database; four regression models were constructed in which the number of missed working hours per year was the dependent variable, and BPH was the reference variable (constant), given that it imposes the lowest PL among investigated diseases. The difference between the four models is as follows; the first two models (models 1 and 2) included all the eleven disease populations with the following independent variables: age, disease duration, EQ-5D-3L index, gender, number of GP visits, and number of outpatient visits. While the latter two models (models 3 and 4) excluded diabetes patients while utilizing two additional independent variables (i.e. informal care and education level). Models 1 and 3 used the full patient population, while models 2 and 4 only used patient populations under 64 years old, which is the average retirement age in Hungary (Simonovits, 2011) simulating the working population within our sample.

VII.2. Results

VII.2.1. Characteristics of studies

Three of the eleven COI studies were published in Hungarian language and eight in English. Patient sample sizes ranged between 68 (multiple sclerosis) and 480 (diabetes), while the total

population comprised 1,888 patients, including 1,222 patients who were of working age (under 64). The predominant productivity valuation approach adopted was the HCA, with one paper using both HCA and FCA together. For all eleven studies, the opportunity cost method was employed using the national gross average wage for the study year. Simple open question was the dominant PL measurement method, with only two COI studies using the WPAI questionnaire. The characteristics of the investigated COI studies are summarised in table 11.

VII.2.2. Demographic results of patient populations

Table 12 summarises the demographics, health status, and health care resource use for each disease. Overall, patients average age ranged between 36 and 77 years. Female population comprised roughly half of the total population, with highest percentage among systemic sclerosis patients, and lowest in psoriasis (apart from BPH). Higher education levels were noticed among multiple sclerosis patients, while schizophrenia patients reported the lowest educational levels. Health status score was highest in BPH and lowest in dementia patients, while psoriasis patients had the longest disease duration. In resource use, schizophrenia patients visited outpatient clinics more frequently than other chronic diseases, while systemic sclerosis patients were highest in GP visits, and were admitted to hospitals more frequently than other chronic disease patients.

Regarding disease-specific PL, highest mean of lost productive hours was attributed to schizophrenia with a yearly average of 1,660 lost hours per patient, followed closely by musculoskeletal diseases (i.e. rheumatoid arthritis and systemic sclerosis). BPH, on the other hand, caused the lowest lost productive hours per year among the investigated chronic illnesses. This reflected on the yearly indirect cost means with schizophrenia on top (9,912 euros) followed closely by rheumatoid arthritis, while BPH embarked the lowest indirect costs across the investigated chronic diseases. Similarly, the average indirect cost as a percent of GDP/capita was highest in schizophrenia and rheumatoid arthritis, while lowest in BPH. Lost productive hours and cost means are summarised in Table 12, while Figure 16 shows a bar chart of indirect cost as a percentage of GDP/capita for each investigated chronic disease.

Table 11. Characteristics of the included COI studies; language, costing year, PL methods, gross income, and wage rate. *Source: (Rashdan & Brodszky, 2020)*

Disease	Reference	Language	Costing Year	Measurement method of productivity loss hours	Presenteeism inclusion	Valuation of productivity loss (HCA, FCA, Both)	Gross income at costing year (Euro/Month)	Gross Wage Rate to 2018 (%) *
Benign prostatic hyperplasia	(Rencz et al.)	English	2014	WPAI	Yes	HCA	989	95.6
Dementia	(Érsek et al.)	English	2007	Open Question	No	HCA	993	96.0
Diabetes	(Jermendy et al., 2017)	Hungarian	2003	Open Question	No	HCA	653	63.1
Epilepsy	(Pentek et al., 2013)	Hungarian	2009	Open Question	No	HCA	957	92.5
Multiple Sclerosis	(Pentek et al., 2012)	English	2009	Open Question	No	HCA	957	92.5
Parkinson's disease	(Tamás et al., 2014)	English	2009	Open Question	No	HCA	957	92.5
Psoriasis	(Balogh et al., 2014)	English	2012	WPAI	No	Both	1,054	101.9
Psoriatic arthritis	(Brodszky et al., 2009)	English	2007	Open Question	No	HCA	996	96.3
Rheumatoid arthritis	(Márta Péntek et al., 2007)	English	2004	Open Question	No	HCA	490	47.4
Schizophrenia	(M Péntek et al., 2012)	Hungarian	2009	Open Question	No	HCA	957	92.5
Systemic sclerosis	(Minier et al., 2010)	English	2006	Open Question	No	HCA	913	88.3

* Average nominal gross wage in 2018 in Hungary was 1034.5 euros (Source: Hungarian Statistical Office website (Hungarian Central Statistical Office, 2018b)).

Table 12. Disease-specific demographics, annual resource use, health status, adjusted indirect cost, and indirect cost as a percent of the total cost. *Source: (Rashdan & Brodszky, 2020)*

Disease name	Total number of patients	Number of patients below 64	Age mean (95% C.I.)	Higher education patients N (%)	Females N (%)	EQ-5D-3L Index (95% C.I.)	Disease duration in years (95% C.I.)	Number of outpatient visits mean (95% C.I.)	Number of GP visits mean (95% C.I.)	Number of hospital admissions mean (95% C.I.)	Number of missed working hours per year mean (95% C.I.)	Adjusted indirect (PL) cost in Euros (2018 rates)	Adjusted total cost in Euros (2018 rates)	Indirect (PL) Cost as a percent of total cost
Benign prostatic hyperplasia	246	49	70.59 (69.56, 71.61)	74 (30%)	0 (0.0)	0.85 (0.83, 0.88))	5.56 (4.95, 6.18)	6.60 (5.63, 7.57)	1.04 (0.63, 1.45)	1.08 (0.97, 1.19)	35.67 (7.42, 63.92)	213.01, (44.28, 381.74)	917.21, (676.95, 1157.46)	23.2%
Dementia	88	6	77.55 (75.75, 79.37)	12 (14%)	52 (59.1)	0.39 (0.32, 0.46)	4.32 (3.11, 5.53)	1.15 (0.85, 1.44)	0.85 (0.64, 1.07)	0.11 (0.05, 0.18	104.65 (29.26, 180.04)	624.51, (174.61, 1074.40)	4159.21, (2490.39, 5828.03)	15.0%
Diabetes	480	331	52.56 (51.08, 54.05)	N/A	267 (55.6)	0.77 (0.74, 0.79)	15.60 (13.72, 15.48)	5.45 (5.02, 5.88)	7.29 (6.69, 7.89)	N/A	187.99 (138.04, 237.94)	1121.2, (823.31, 1419.11)	2433.36, (2130.67, 2736.07)	46.1%
Epilepsy	100	97	36.65 (34.16, 39.14)	18 (18%)	58 (58.0)	0.78 (0.74, 0.86)	15.45 (13.04, 17.87)	3.52 (2.63, 4.41)	3.27 (2.25, 4.28)	0.44 (0.11, 0.76)	214.96 (135.62, 294.29)	1283.94, (810.05, 1757.79)	2617.55, (1920.52, 3314.57)	49.1%
Multiple sclerosis	68	67	37.96 (35.74, 40.17)	28 (42%)	48 (70.6)	0.67 (0.60, 74)	7.02 (5.55, 8.48)	3.02 (2.16, 3.87)	1.33 (0.80, 1.86)	0.49 (0.32, 0.65)	405.61 (225.93, 585.28)	2422.67, (1349.48, 3495.85)	11786.35, (9980.34, 13592.36)	20.6%
Parkinson's disease	110	55	63.28 (61.15, 6541)	40 (36%)	36 (32.7)	0.58 (0.52, 0.63)	8.22 (7.10, 9.33)	4.86 (3.77, 5.96)	3.22 (2.41, 4.03)	0.42 (0.28, 0.55)	381.20 (227.21, 535.20)	2276.91, (1357.12, 3196.69)	6518.57, (5248.36, 7788.8)	34.9%
Psoriasis	200	157	50.66 (48.83, 52.50)	40 (20%)	64 (32.0)	0.69 (0.65, 74)	21.44 (19.80, 23.08)	1.61 (1.24, 1.98)	4.26 (3.05, 5.47)	1.72 (1.65, 1.78)	206.4 (126.8, 286.0)	1231.85, (756.86, 1706.85)	8728.09, (7505.24, 9950.93)	14.1%
Psoriatic arthritis	183	149	50.15 (48.25, 52.04)	43 (24%)	105 (57.4)	0.47 (0.42, 52)	9.24 (7.89, 10.59)	6.38 (5.25, 7.52)	3.70 (2.87, 4.54)	0.64 (0.51, 0.78)	505.21 (380.88, 629.53)	3015.11, (2273.13, 3757.08)	5787.76, (4644.17, 6931.34)	52.1%
Rheumatoid arthritis	255	182	55.45 (53.93, 56.97)	42 (17%)	218 (85.5)	0.46 (0.42, 0.50)	9.10 (7.92, 10.27)	7.78 (6.87, 8.70)	8.99 (8.11, 9.87)	1.09 (0.93, 1.25)	1636.69 (1389.78, 1883.59)	9763.06, (8290.25, 11235.86)	14489.14, (12877.05, 16101.24)	67.4%
Schizophrenia	78	73	44.24 (41.30, 47.19)	9 (12%)	36 (46.2)	0.64 (0.57, 0.71)	N/A	14.91 (11.26, 18.56)	1.76 (0.57, 2.94)	N/A	1659.56 (1474.66, 1844.46)	9912.5, (8808.1, 11016.22)	15003.52, (13308.88, 16698.17)	66.1%
Systemic sclerosis	80	56	57.39 (55.25, 59.52)	16 (20%)	72 (90.0)	0.58 (0.52, 0.64)	7.16 (5.69, 8.64)	7.14 (5.44, 8.83)	10.26 (8.92, 11.60)	4.61 (3.94, 5.29)	1023.02 (789.94, 1256.11)	6103.74, (4713.06, 7494.42)	10893.16, (9269.18, 12517.12)	56.0%
Total	1888	1222	55.17 (54.44, 55.91)	248	956 (50.6)	0.66 (0.64, 0.67)	11.40 (10.92, 11.88)	5.64 (5.32, 5.97)	4.74 (4.44, 5.04)	1.15 (1.06, 1.25)	509.32 (460.06, 558.59)	2464.03, (2243.12, 2684.95)	5684.59, (5338.09, 6031.1)	43.3%

* NA: Data not available

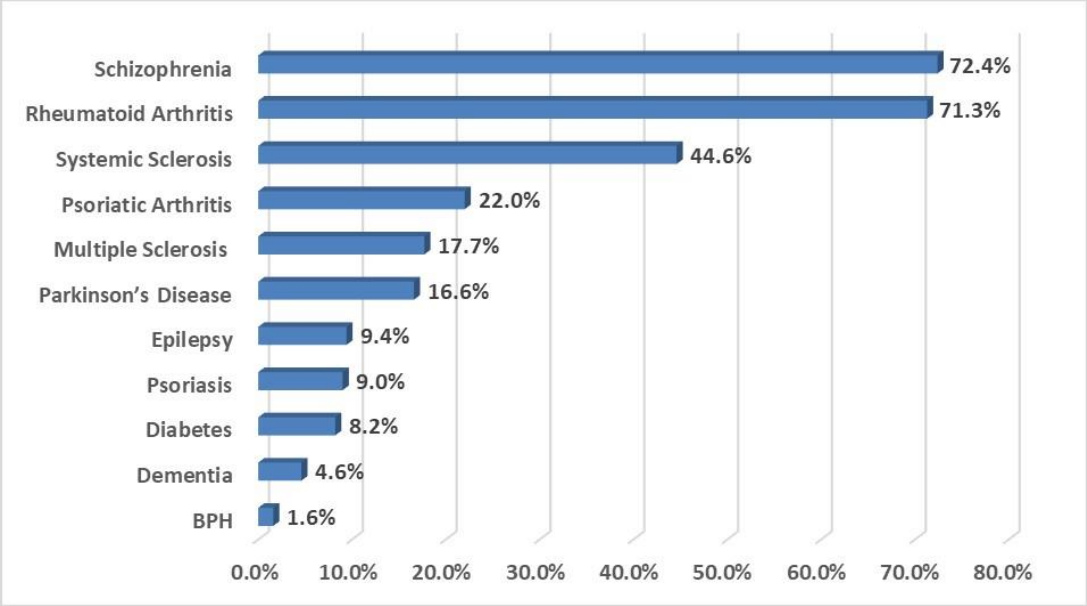


Figure 16. indirect cost as a percentage of GDP/capita for eleven NCDs in Hungary. *Source: (Rashdan & Brodszky, 2020)*

VII.2.3. PL Drivers by disease

Table 6 shows the association of PL with demographic, resource use, and health status variables. ANOVA analysis of disease PL means revealed that gender differences were significant only in diabetes and epilepsy, while higher education levels resulted in significant PL in BPH, rheumatoid arthritis, and schizophrenia patients. In resource use, we found that a higher number of hospital admissions is significantly associated with higher PL in BPH, dementia, multiple sclerosis, Parkinson's disease, psoriasis, psoriatic arthritis, and rheumatoid arthritis patients, while it significantly decreases PL in psoriasis patients. A higher frequency of GP visits was a significant driver for PL in Parkinson's patients, whereas the number of outpatient visits was a significant PL driver in epilepsy and psoriatic arthritis patients. Similarly, patients who received informal care reported significant PL in epilepsy, multiple sclerosis, and psoriatic arthritis. Similar but no significant differences were observed in all other diseases for informal care use. Overall, resource use variables -while significant- correlated positively towards lost productive hours, with the number of hospital admissions as the dominant resource use, indirect cost driver.

In health status, the EQ-5D-3L index significantly correlated negatively with PL in diabetes, epilepsy, multiple sclerosis, psoriatic arthritis, and rheumatoid arthritis imposing lower PL with higher scores. As for age impact on PL, patient populations under 64 correlated positively with PL in diabetes, epilepsy, and schizophrenia, while correlated negatively with Parkinson's disease patients (due to high average age). On the other hand, when the whole patient population of all ages was considered, age correlated positively with epilepsy and systemic sclerosis, whereas correlated negatively with BPH, Parkinson's disease, psoriatic arthritis, and rheumatoid arthritis patients.

VII.2.4. Weighted regression modelling

For our statistical modelling, the multicollinearity test results for the regression variables revealed no variance inflation factor (VIF) value above 5. The homogeneity assumption of our dependent variable was tested using Levene's test of homogeneity and concluded the inequality of our variances (p-value < 0.00). Bootstrapping with 2000 repetitions was employed to account for the homogeneity assumption violation as well as the normality assumptions violation as shown by other filed researchers (Hansen, Evans, & Shultz, 1999; Krishnamoorthy, Lu, & Mathew, 2007).

Four predictive models were constructed with resulting R squared values of 0.354, 0.404, 0.367, 0.420 for models 1-4 respectively. The resulting unstandardized beta coefficients and their corresponding significance for our models are presented in table 7. In model 1, older age and better health status (EQ-5D-3L index) significantly decrease PL. Patients with diabetes, epilepsy, or psoriasis also significantly contribute to decreasing PL. On the other hand, longer disease duration and more frequent GP visits, along with being a BPH, rheumatoid arthritis, schizophrenia, or a systemic sclerosis patient, all significantly contribute to increasing PL. In contrast, for model 2 (under 64), longer disease duration, more frequent GP and outpatient visits, along with being a rheumatoid arthritis, schizophrenia, or a systemic sclerosis patient, all significantly contribute to increasing PL, while only higher health status scores (EQ-5D-3L index) decrease PL in the working population.

In model 3, older age, higher education, and better health status (EQ-5D-3L index), in addition to patients with epilepsy, multiple sclerosis, or psoriatic arthritis, all significantly contribute to decreasing PL. On the other hand, longer disease duration, informal care utilisation, along with being a BPH, rheumatoid arthritis, schizophrenia, or a systemic sclerosis patient, all significantly increase PL. In contrast, in model 4 (under 64), longer disease duration, informal care utilisation, in addition to being a rheumatoid arthritis, schizophrenia, or a systemic sclerosis patient, significantly contribute to increasing PL, while only higher education and health status scores (EQ-5D-3L Index) decrease PL in the working population.

Table 13. Disease-specific drivers of PL (hours lost/year) with demographics, resource use, and health status indicators. *Source: (Rashdan & Brodszky, 2020)*

Disease Name	Correlation with lost productive hours						Gender		Education		Informal care	
	GP visit	Hospital admissions	Outpatient visits	EQ-5D-3L Index	Age (all)	Age (<64)	Female (Male)	P	Higher (Lower)	P	Received (Did not receive)	P
	Spearman's rho (P)						Lost hours mean	ANOVA	Lost hours mean	ANOVA	N (%)	ANOVA
Benign Prostatic Hyperplasia	-0.027 (0.677)	**0.962 (0.000)**	-0.010 (0.881)	0.116 (0.074)	**-0.321 (0.000)**	-0.107 (0.465)	N/A 35.67	N/A	**78.71 (17.25)**	**0.050**	0.0 (38.15)	0.513
Dementia	-0.001 (0.990)	**0.275 (0.010)**	0.082 (0.447)	-0.074 (0.495)	0.118 (0.276)	N/A*	136.88 (59.76)	0.327	26.50 (116.99)	0.416	120.83 (13.35)	0.358
Diabetes	0.040 (0.416)	N/A	-0.085 (0.064)	**-0.232 (0.000)**	0.001 (0.985)	**0.133 (0.014)**	**131.17 (259.12)**	**0.012**	N/A	N/A	N/A	N/A
Epilepsy	0.203 (0.073)	0.199 (0.068)	**0.197 (0.050)**	**-0.531 (0.000)**	**0.448 (0.000)**	**0.488 (0.000)**	**282.62 (121.52)**	**0.046**	64.94 (247.89)	0.079	**739.62 (118.55)**	**0.000**
Multiple sclerosis	0.240 (0.051)	**0.428 (0.000)**	0.219 (0.079)	**-0.306 (0.011)**	0.231 (0.060)	0.231 (0.060)	416.13 (380.36)	0.858	250.33 (474.17)	0.211	**856.11 (143.69)**	**0.000**
Parkinson's Disease	0.234 (0.14)	**0.207 (0.030)**	0.066 (0.492)	-0.141 (0.160)	**-0.567 (0.000)**	**-0.421 (0.001)**	366.97 (385.72)	0.911	277.38 (440.53)	0.315	522.24 (254.76)	0.086
Psoriasis	-0.011 (0.873)	**-0.256 (0.000)**	0.049 (0.498)	-0.112 (0.121)	-0.137 (0.056)	-0.040 (0.614)	315.07 (155.25)	0.065	85.52 (236.61))	0.135	227.38 (204.19)	0.867
Psoriatic Arthritis	**0.197 (0.008)**	**0.173 (0.019)**	**0.136 (0.066)**	**-0.196 (0.009)**	**-0.164 (0.028)**	0.059 (0.468)	526.24 (476.89)	0.700	410.30 (537.79)	0.394	**731.76 (368.08)**	**0.005**
Rheumatoid Arthritis	**0.255 (0.000)**	**0.124 (0.049)**	0.116 (0.068)	**-0.131 (0.040)[a]**	**-0.401 (0.000)**	-0.132 (0.073)	1629.39 (1726.37)	0.788	**522.51 (1879.07)**	**0.000[a]**	1763.58 (1510.80)	0.314
Schizophrenia	-0.035 (0.761)	N/A	0.054 (0.639)	**-0.226 (0.046)**	0.110 (0.340)	**0.424 (0.000)**	1646.23 (1670.99)	0.895	**1155.25 (1725.34)**	**0.049**	1819.52 (1588.47)	0.253
Systemic Sclerosis	-0.005 (0.968)	0.207 (0.066)	0.056 (0.622)	-0.153 (0.176)	**0.284 (0.011)**	-0.206 (0.127)	1077.39 (533.73)	0.165	993.62 (1030.37)	0.901	1131.18 (954.60)	0.466

*NA: not available/applicable a: Hypothesis testing results (H3)

Table 14. Weighted Linear Regression models 1-4. Variables unstandardized B coefficients along with their corresponding significance vale. (results are significant at p<0.05).

Weighted linear regression (WLS)								
	Model 1 (All patients)		**Model 2 (patients <64)**		**Model 3 (All patients)**		**Model 4 (patients <64)**	
	Unstandardized Coefficients	P	Unstandardized Coefficients	P	Unstandardized Coefficients	P	Unstandardized Coefficients	**P**
	B		B		B		B	
Constant	**1238.037**	**.000**	364.536	.145	**1367.792**	**.000**	386.283	.181
Age	**-12.788**	**.000**	2.530	.361	**-15.064**	**.000**	2.047	.542
Gender	53.515	.273	60.597	.320	66.489	.250	67.942	.349
Disease duration	**11.971**	**.000**	**15.406**	**.000**	**11.965**	**.000**	**14.627**	**.001**
High education	-	-	-	-	**-166.925**	**.006**	**-255.823**	**.001**
Number of GP visits per year	**9.920**	**.020**	**11.619**	**.021**	5.506	.280	7.938	.186
Number of outpatient visits per year	3.954	.169	**7.767**	**.026**	4.181	.200	7.510	.058
Received Informal care	-	-	-	-	**209.539**	**.001**	**273.607**	**.001**
EQ-5D-3L index	**-473.004**	**.000**	**-521.625**	**.000**	**-390.339**	**.000**	**-408.674**	**.000**
Dementia	-54.327	.624	-523.890	.126	-198.042	.126	-705.805	.066
Diabetes	**-322.717**	**.006**	-208.146	.295	-	-	-	-
Epilepsy	**-427.851**	**.001**	-135.420	.499	**-541.018**	**.000**	-211.540	.356
Multiple sclerosis	-183.109	.135	103.524	.591	**-318.283**	**.026**	13.168	.952
Parkinson's disease	90.051	.385	375.498	.052	35.475	.762	314.245	.146
Psoriasis	**-383.147**	**.001**	-282.779	.150	**-430.304**	**.002**	-308.265	.167
Psoriatic arthritis	-55.996	.619	126.273	.503	-141.194	.270	61.999	.770
Rheumatoid arthritis	**1190.580**	**.000**	**1550.241**	**.000**	**1102.364**	**.000**	**1453.579**	**.000**
Schizophrenia	**1061.936**	**.000**	**1308.953**	**.000**	**932.835**	**.000**	**1196.595**	**.000**
Systemic sclerosis	**529.563**	**.000**	**919.060**	**.000**	**466.638**	**.000**	**846.501**	**.000**
R squared	0.354		0.404		0.367		0.420	
Adjusted R squared	**0.347**		**0.395**		**0.358**		**0.407**	

*Excluded variables from each model are indicated by a dash. - Constant is BPH dummy.

VII.3. Discussion

This work presents the largest set of NCD indirect cost estimates in the CEE region. PL data from eleven COI studies have been pooled, normalised, and compared to reflect each disease's current total and indirect cost estimates; and were further presented using internationally transferrable monetary terms (i.e. PL as a proportion of GDP/capita). Significant health care resource use, health status, and demographic variables driving PL in chronic disease patients were also identified and quantified. Our PL correlation results infer that a better health status score did not have a consistent reduction impact on PL on all investigated NCDs (e.g. BPH) and had insignificant associations with dementia, multiple sclerosis, psoriasis. On the other hand, in resource use, the number of hospital admissions was the highest contributor towards increased PL in most of the investigated chronic diseases. This is mainly attributed to the fact that a hospital admission is indicating a more severe disease than other resource use indicators employed in our analysis (i.e. GP visit, outpatient visit). Age, on the other hand, had mixed PL impacts, depending on the disease type as well as the age group investigated (under or above 64 years). Although the difference in gender PL means was apparent in most diseases, yet it was inconsistent for specific sex (e.g. diabetes and epilepsy). Similar discrepancies apply for educational level association with PL. Rheumatoid arthritis patients (musculoskeletal disease) showed significant association with educational level as well as the health status concluding the acceptance of our hypothesis (H3).

WLS modelling revealed that only health status score (i.e. ED-5D-3L) had a consistently significant negative impact on PL (decreasing lost productive hours) across all four models. Similarly, in models where education level was accounted for (i.e. models 3, 4), a significant decrease in PL was observed with higher educational levels. This was addressed by Zimmerman, Woolf, and Haley (2015) who investigated higher education impact on overall health and proposed a hypothesis that adults with

relatively higher levels of education, tend to have greater socio-economic resources to pursue a healthy lifestyle, and that they can also be better equipped with the health literacy level required to draw on later in their lives. As for gender's role in PL modelling, none of our four predictive models flagged gender as a significant PL variable. Rather, the main contributor in all of our four models was being a patient of one of the three most cost-intensive diseases (i.e. schizophrenia and musculoskeletal diseases).

In 2012, the WHO announced Chronic disease as one of the major challenges facing nations worldwide in the current century (D. Bloom et al., 2011; *Third Copenhagen Consensus Outcome Document*, 2012). Currently, the responsibility of providing healthcare services in Hungary for primary care, outpatient care, and inpatient care lies within the government, whereas the direct responsibility for financing healthcare services is managed by the national health insurance fund administration (NHIFA) (Gulácsi et al., 2009). It is mandatory for all citizens living in Hungary to take out national health insurance; however, private insurance policies can be bought as well (Nolte, Knai, & Saltman, 2015). Current Hungarian health economic guideline recommends the analysis to be conducted from the health care system perspective and later mentions that a societal perspective is only optional (Szende et al., 2002).

Our results emphasise that indirect costs can comprise a large portion of the total economic burden of NCDs. Health policymakers -often- disregard indirect costs due to various reasons, such as the scarcity and complexity of available local evidence to adopt a societal perspective. Moreover, the weak international transferability of health economic results further imposes more hurdles. Heterogeneity of COI reporting is a major issue in results transferability, mainly arising from the lack of methodological consensus on perspective, measurement instruments, study designs, and valuation methodologies among other reasons (Onukwugha et al., 2016). Devising one universal reporting method for all diseases can be farfetched given the diverse nature of diseases. On the other hand, proposals for the standardisation of COI reporting

methodologies for a specific disease although still scarce yet are starting to emerge. Jin and Mosweu (Jin & Mosweu, 2017) for instance, proposed a specific set of recommendations for schizophrenia COI reporting and valuation methods. This was done by conducting a systematic review in which, they gathered and analysed a sufficient number of schizophrenia COI results from multiple authors and countries, to finally come to a consensus for a standard COI reporting methodology for schizophrenia.

Although indirect cost as a proportion of total cost has been often reported in health economic evaluations (Le et al., 2018; Thienpont, Paternostre, & Van Wymeersch, 2015), yet this measure has proven to be inadequate to facilitate the interregional or even intraregional transferability of the results. For instance, Jin and Mosweu (Jin & Mosweu, 2017) reviewed and extracted this ratio for schizophrenia from multiple COI studies, and demonstrated how the results varied greatly across different countries, and even within the same country occasionally. Schizophrenia's indirect cost percentage of total cost fluctuated from as low as 36% (in Norway) as reported by Evensen et al. (2015), up to 83% in South Korea, as reported by Chang et al. (2008). While our costs for schizophrenia resulted in a 66% indirect cost proportion from the total cost. Similarly, Blahova et al. (Blahova Dusankova, Kalincik, Dolezal, Kobelt, & Havrdova, 2012) published a COI study for multiple sclerosis costs in the Czech Republic with a resulting proportion of 45% indirect costs out of total costs in comparison to our reported 20%. Hence, it is apparent that the measure, "indirect cost/total cost" concludes major international discrepancy and can render the transferability of the results unfeasible.

To address the transferability issue and building on the assumption that higher-income countries typically possess a higher capacity to spend on their health systems and vice versa; it can be beneficial for indirect costs to be formulated taking into consideration a national GDP perspective. The measure of indirect cost proportion out of the

national GDP/capita can potentially prove more beneficial for PL results transferability than “indirect cost/total cost”.

To further simplify the “indirect cost/(GDP/capita)” utilisation, a three-level categorisation system is proposed; high PL (Above 50%), moderate PL (15%-50%), and low PL (Below 15%). The highest cap was proposed as 50% of the individual’s productive capacity is lost due to those illnesses. For instance, our findings demonstrated that schizophrenia and rheumatoid arthritis, both fall within the “high PL” disease category. Systemic sclerosis, multiple sclerosis, Parkinson’s disease, and psoriatic arthritis, all fall within the “Moderate PL” category. While dementia, diabetes, epilepsy, psoriasis, and BPH patients fell into the “low PL” category. Musculoskeletal disease was almost on par with mental disease in terms of lost productivity. In a similar methodological approach, Zhao et al. (2013) conducted a cross-country secondary analysis for the COI studies which reported indirect costs using the HCA for a few chronic diseases; one of which was schizophrenia. Their analysis comprised 9 schizophrenia COI studies, and the GDP-adjusted indirect costs were statistically synthesised so that the indirect costs are presented as a percentage of the national gross domestic product per capita “indirect cost/(GDP/capita)” using different models. Three different indirect cost/(GDP/capita) means (95 % CI) were reported (i.e. 66.5% (66.0–67.0), 79.2% (54.0–104.3), 79.2% (52.4–117.8), based on three modelling approaches (i.e. fixed-effect model, random-effect model and bootstrapping estimation) respectively. all three reported indirect cost/(GDP/capita) means are fairly close to our reported result for schizophrenia (72.4%), and all are falling into the “high PL” category. This demonstrates the usefulness of the national GDP association with indirect costs for international societal costs visualisation.

In light of our transferability aim, and provided that our results concluded a significant association between health status and educational level with PL, we presume that incorporating extra adjustment measures over and above the GDP/capita indicator to address local population specificities, such as the human capital index (HCI) and

health expenditure (HE), can be beneficial in transferring PL costs between regions. In the following chapter, we investigate the usefulness of different economic indicators and methods in PL costs transferability. Moreover, given that musculoskeletal diseases have been categorised into the high PL disease category, we chose to test our transferability hypotheses using musculoskeletal disease PL costs given the disease's significance among other NCDs in addition to the regional need.

Some limitations of this study should be highlighted. First, disease severity and co-morbidity data were not taken into consideration. Second, in our PL modelling for working patient populations (models 2 and 4), some moderate PL diseases (e.g. dementia and Parkinson's disease) could be under-represented in these models given their late age disease nature. Third, most of the studies were conducted in tertiary clinical centres, and systematic selection bias due to centre effects could have been present. Thus, the results may not be representative of the entire disease population. Finally, study data were collected retrospectively using self-completed questionnaires and, with such data, there is always a risk of recall bias.

VIII. REGIONAL ESTIMATES AND TRANSFERABILITY OF PRODUCTIVITY LOSS COSTS IN MUSCULOSKELETAL DISEASE: V4 TO MENA

Provided the recent emphasis on rational distribution of healthcare resources, both the availability and need for health economic evaluations are expected to spike to match that demand. However, in LMICs the scarcity of health economic evaluations is still a major issue as demonstrated in our previous chapters. Apart from the substantial resources required to attain national self-sufficiency in health economic evaluations, it's no doubt that considerable delays are expected, rendering the potential benefits and savings much further in the future. In that sense, even attaining reference estimates for specific patient populations can provide leverage for decision-makers in budget allocations both on the long and medium term.

In our previous chapter, the significant impact of indirect costs due to musculoskeletal disease has been demonstrated to be among the highest contributors to societal PL. it was also discussed that musculoskeletal diseases are among the MENA's top priorities (Institute for Health Metrics and Evaluation; Human Development Network; The World Bank, 2003; Mokdad, 2014). We also noticed how the presentation of PL costs as a percent of GDP/capita may be a useful indicator for results transferability as was confirmed by (Gao et al., 2016) for direct disease costs. On the other hand, fewer authors have addressed the transferability of indirect costs in a similar manner. (Zhao et al., 2013) investigated the aspects that contribute to disease indirect costs variance globally by pooling and analysing the costs of specific disease populations. Although the estimates standard deviations were quite wide since no geographical constraints were set to his filters, yet his findings did strongly suggest the feasibility and usefulness of the construction of a universal reference range for PL costs of a specific disease, presenting the cost as a proportion of national GDP/capita.

In an attempt to provide more precise PL estimates, we assume that pooling of costs from a single region with similar domestic output, under similar political and health

systems, can be beneficial in attaining a more precise cost estimate for a confined disease group. In this chapter, we specifically chose the V4 rather than the whole CEE as a source, given the convergence in income and expenditure levels within the member countries compared to the other CEE countries. We assume that cross-country PL cost differences are negligible among the V4 members. Hence, expect to find insignificant differences in musculoskeletal disease PL cost estimates between countries within the same region (H4).

Moreover, a discrepancy in transferring direct and indirect costs is undeniable and expected. This is attributed to many reasons, among which is the essential difference between direct and indirect cost components and measurement methods. Direct cost components (e.g. hospitalisation cost, outpatient visit, medication cost) are valued on a different basis than human productivity loss components (such as absenteeism, presenteeism), as the latter is concerned with the local human capital preparedness and their specific output capacity, rather than a tangible good or service. Moreover, our previous chapter identified education and health status as significant determinants in PL costs. We assume that incorporating the Human capital index (HCI) as an additional adjustment factor, can increase the precision of cross-region PL costs transfer than sole GDP/capita adjustment (H5).

Other reasons for the discrepancy between direct and indirect costs may arise from the significant differences in national systematic management aspects such as disability management, early retirement protocols in addition to overall spending capacities. In an attempt to normalise those issues, we assume that adjusting for health expenditure (HE) differences can aid further in generating more precise international disease cost estimates when coupled with GDP/capita (H6). Furthermore, to set contrast for our GDP-based adjusted methods, we test the usefulness of two wage-based adjustment methods; PL hours back calculation and wage ratio adjustment.

In this chapter, we aim to provide a precise regional estimate for musculoskeletal disease Indirect costs for the V4, stratified by PL cost item type and adjusted to reflect current euro value. We proceed further and test the transferability of those pooled PL costs from the V4 region into the MENA, through which we test the usefulness of different adjustment approaches for enhanced PL costs interregional estimates.

VIII.1. Methods

We split our methodological section into four parts: first, is the systematic identification and extraction of musculoskeletal PL costs from the V4, followed by the indicator's sources and utilisation in costs normalisation, right before the regional adjustment formulas and sensitivity testing methods for the MENA region.

VIII.1.1. V4 Musculoskeletal PL costs identification

Diseases defined by the ICD-10 Chapter XIII (i.e. Diseases of the musculoskeletal system and connective tissue) with diagnosis codes between M00-M99 were systematically acquired following other authors' identification rationale (Ahlberg, 2014). PRISMA guidelines were applied were possible (Alessandro Liberati et al., 2009). A combination of keywords was devised to identify health economic evaluations for musculoskeletal and connective tissue disease, reporting any sort of indirect costs from the V4 countries. Mesh terms were used for disease designations while a comprehensive combination of keywords was devised to account for PL costs and V4 countries. PubMed was selected as the source database, the search was done on March 4th 2021, and the search was targeted for journal articles published in English language with full text available. The search code used is shown in table 15.

Table 15. PubMed search code

(((musculoskeletal diseases[MeSH Terms]) OR ("connective tissue disease"[MeSH Terms])) AND ("indirect cost"[Title/Abstract] OR "indirect costs"[Title/Abstract] OR "in-direct cost"[Title/Abstract] OR "productivity"[Title/Abstract] OR "productive hours"[Title/Abstract] OR "productivity loss"[Title/Abstract] OR "lost productive hours"[Title/Abstract] OR "lost productivity"[Title/Abstract] OR

("productivity"[Title/Abstract] AND "loss")[Title/Abstract] OR ("productivity"[Title/Abstract] AND "lost")[Title/Abstract] OR "absenteeism"[Title/Abstract] OR "presenteeism"[Title/Abstract] OR "opportunity cost"[Title/Abstract] OR "friction cost"[Title/Abstract] OR "income loss"[Title/Abstract] OR "work time"[Title/Abstract] OR "sick leave"[Title/Abstract] OR "time off work"[Title/Abstract] OR "time away"[Title/Abstract] OR "time lost"[Title/Abstract])) AND ("hungary"[Title/Abstract] OR "hungarian"[Title/Abstract] OR "hungar"[Title/Abstract] OR "magyar"[Title/Abstract] OR ("czech"[Title/Abstract] AND "republic")[Title/Abstract] OR "czech"[Title/Abstract] OR "Slovakia"[Title/Abstract] OR "Slovak"[Title/Abstract] OR "slavic"[Title/Abstract] OR "Poland"[Title/Abstract] OR "polish"[Title/Abstract] OR "polska"[Title/Abstract])

VIII.1.1.1. Inclusion criteria

The initial inclusion/exclusion for the articles was implemented by first screening for eligibility from the articles' title and abstract. Full-text was then acquired and evaluated in detail against the following eligibility criteria:

- English language journal articles reporting original research on humans, involving the local population from the target V4 countries with full text available.
- Full or partial health economic analysis.
- Reporting indirect/PL costs in annual per patient terms, or can be calculated without statistical management (e.g. per month cost multiplied by 12 to simulate a year)
- Using the Human capital approach (HCA) in calculating PL burden.

Conference proceedings, reviews, methodological papers, commentaries, non-original research, or studies that reported any type of indirect costs without a clear methodological sequence were all excluded. References of included papers were finally swiped to identify other relevant research that might report Musculoskeletal PL costs.

VIII.1.1.2. Data extraction

A Microsoft Excel spreadsheet was developed according to a predefined criterion for data collection. From the included articles, we extracted reported PL/indirect cost items along with their description, currency, costing year, number of patients, study type (primary/secondary), data source (hospital/insurance), data collection method (database/survey), as well as PL cost item category as per table 2 (literature review chapter). When studies reported indirect costs using multiple economic indicators, GDP-based costs were extracted. For studies that reported specific PL costs for each severity level, the average cost for all severity levels was used or calculated if not provided. Similarly, the average was calculated if PL costs were stratified by age. When informal care costs were included in the reported total indirect costs, informal care costs were deducted, and a new total cost item was devised instead.

VIII.1.2. Indicators and costs normalisation

GDP per capita and general government health expenditure as a percent of GDP (HE/GDP) were obtained -whenever possible- from a single source (i.e. World Economic Outlook Database). USD values were converted into their 2020 Euro equivalent (2020 Conversion rate 1 USD= 0.877 Euro). Country-specific HCI was obtained directly from the world bank website. All indicators were matched to their corresponding costing year for each cost item. All indicators were for the year 2020 except for HE/GDP which was for the year 2019 as 2020 data has not been disclosed yet (probably because of COVID-19 impact). National average wages for cost year were either obtained from the study itself or extracted national statistical office or a third party, respectively.

Tunisia's official average salary data were not officially, nor freely available, and historical estimates can be invalid in the time being due to currency fluctuations. The average salary was obtained from a grey literature source (i.e. http://www.salaryexplorer.com/) where the average monthly salary for 2020 was 3,910 TND (1196.24 euros). It is worth noting that while the GDP/capita of Tunisia

is roughly one quart of that of any V4 country, yet the monthly average salary is quite comparable (Hungary:1105 euros, Poland: 1237 euros).

Raw PL costs were normalised in value by converting each cost item (if not provided directly) into its corresponding costing year Euro value using country and year specific exchange rates obtained from (https://www.exchangerates.org.uk/). Costs were then further adjusted for Inflation to reflect 2020-euro estimates using year-specific inflation ratio (https://www.inflationtool.com) to finally conclude the normalised costs in 2020-euro value.

VIII.1.3. Regional adjustment methods

Below are the five MENA transferability approaches we test in this chapter, the calculations were done on an individual cost item level, after the normalization to reflect 2020 euro values, except for method 1 where the costs were used as is without normalisation given the specificity of PL for that year. Methods 1 and 4 are wage-based adjustment methods, while methods 2, 3, and 5 are GDP-based adjustment methods.

1. Method 1: (Reverse calculation of lost productive hours)
    - (PL cost per patient per year/12/168) = PL cost per patient per hour at the source country at costing year
    - (average gross monthly wage at costing year /168 hours)$_{V4}$ = average hourly wage$_{V4}$
    - (PL cost per hour /average hourly wage) = number of lost productive hours
    - Number of lost hours * (average gross monthly income 2020/168 hours)$_{MENA}$ = MENA PL-hours adjusted cost

2. Method 2: (GDP and HCI adjustment)

- $HCI_{MENA}/HCI_{V4} = HCI_{ratio}$
- (Normalised PL cost / (GDP/capita in V4 $country_{2020}$)) * (MENA $GDP/capita_{2020}$) * (HCI_{ratio}) = <u>MENA GDP and HCI adjusted PL cost</u>

3. Method 3: (GDP adjustment alone)
    - (Normalised PL cost / (GDP/capita in V4 $country_{2020}$)) * (MENA $GDP/capita_{2020}$) = <u>MENA GDP adjusted PL cost</u>

4. Method 4: (International wage adjustment)
    - (Average gross wage in V4 / Average gross wage in $MENA)_{2020}$ * (Normalised PL cost) = <u>MENA wage adjusted PL cost</u>

5. Method 5: (GDP and Health expenditure)
    - $HE_{MENA}/HE_{V4} = HE_{ratio}$
    - (Normalised PL cost / (GDP/capita in V4 $country_{2020}$)) * (MENA $GDP/capita_{2020}$) * (HE_{ratio}) = <u>MENA GDP and HE adjusted PL cost</u>

VIII.1.3.1. Methodological sensitivity analysis

We first used ANOVA to test for significant differences between V4 countries in terms of normalised musculoskeletal disease PL costs (H4). To test the sensitivity of our estimation methods as well as our hypotheses (H5 and H6), we calculate the mean absolute deviation (MAD) between each adjusted cost item, and a reference mean value from the MENA region. Our MENA review of NCDs identified a single evaluation from the MENA region reporting PL costs for musculoskeletal disease (i.e. Ankylosing spondylitis) from Tunisia (Younes et al., 2010). Hence, MAD was calculated for each cost item against our inflation adjusted reference value from Tunisia (i.e. 324.05 Euros per patient per year). Provided the PL type specificity of our reference value, we calculated the MAD for absenteeism cost items only since our PL reference value is due to absenteeism (i.e. sick leave). The method with the lowest

MAD provides the closest estimates, while the precision is governed by the lowest standard error value.

Paired samples t-test was run on the MADs to test for significant differences between similar methods. A significant p-value (sig. <0.05) rejects the test's null hypothesis (i.e. $\mu_{null:}$ true mean MAD difference = 0) and accepts the alternate hypothesis (i.e. $\mu_{alt.:}$ true mean MAD difference $\neq 0$) concluding that the pairs are statistically different from each other. Conversely, an insignificant p-value (sig. > 0.05) indicates that there is no statistical difference between the group means and are rather similar.

VIII.2. Results

Our search for musculoskeletal PL reporting evaluations from the V4 resulted in n=23 articles. After applying full-text journal articles in English language filters the number was brought down to n=13 COI studies, out of which 10 were excluded; n=6 did not report PL costs using the HCA or costs were unclear and could not be calculated for our target countries, n=2 were out of scope, n=1 was a methodology study and n=1 was addressing a sub-population). Further snowballing and reference checking identified 3 more studies which brought up the total number of included studies to n=6 cost of illness studies (COI). Figure 17 shows the Prisma diagram, while table 16 shows the final included n=6 articles. Excluded n=17 articles are listed in appendix IV.

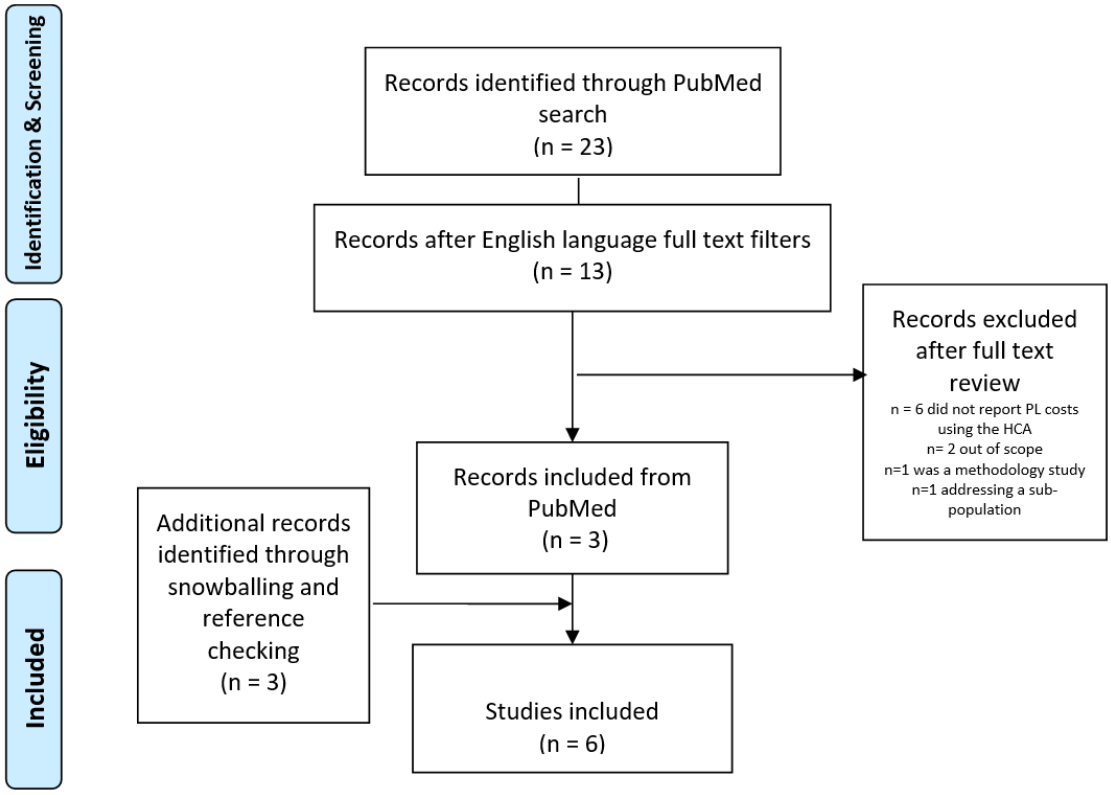


Figure 17. Prisma diagram for the literature review of musculoskeletal disease evaluations reporting productivity costs from the V4.

Table 16. Included studies, their first author, publication year, and reference.

First author	Publication year	Title	Reference
López-Bastida J	2016	Social/economic costs and health-related quality of life in patients with scleroderma in Europe	Eur J Health Econ. 2016 Apr;17 Suppl 1:109-17
Malinowski KP	2016	Indirect costs of absenteeism due to rheumatoid arthritis, psoriasis, multiple sclerosis, insulin-dependent diabetes mellitus, and ulcerative colitis in 2012: a study based on real-life data from the Social Insurance Institution in Poland	Expert Rev Pharmacoecon Outcomes Res. 2016;16(2):295-303
Kawalec PP	2015	The indirect costs of systemic autoimmune diseases, systemic lupus erythematosus, systemic sclerosis and sarcoidosis: a summary of 2012 real-life data from the Social Insurance Institution in Poland	Expert Rev Pharmacoecon Outcomes Res. 2015;15(4):667-73
Minier T	2010	Cost-of-illness of patients with systemic sclerosis in a tertiary care centre	Rheumatology (Oxford). 2010 Oct;49(10):1920-8

Péntek M	2007	Costs of Rheumatoid Arthritis in Hungary	The Journal of rheumatology, 34(6), 1437-1437
López-Bastida J	2016	Social/economic costs and health-related quality of life in patients with scleroderma in Europe	Eur J Health Econ. 2016 Apr;17 Suppl 1:109-17

VIII.2.1. Identified PL cost items - V4

From the included six studies, we acquired a total of (n=25) musculoskeletal disease PL cost items from two countries; Hungary (n=10) and Poland (n=15). No studies from Slovakia or the Czech Republic were included in our analysis since none of their published research met our inclusion criteria. The average total PL cost was 3724.7 (SD: 1707.2) euros for the full sample, with Hungary above the average at 4015.3 (SD: 2283.9) euros compared to Poland 3434.1 (SD: 1347.7) euros. Absenteeism costs showed the highest discrepancy among PL cost types between the countries with an average of 61.9 (SD: 41.5) euros for Hungary, compared to 975.7 (SD: 188.2) euros for Poland. which can be a good reason why average estimates are better than a single estimate. Long-term disability was reported the most with n=7 PL cost items followed by absenteeism n=6 and total PL n=6. Absenteeism and total PL were the only types reported in all studies for both countries. No premature retirement costs were reported in Poland although it was the PL cost item with the highest mean cost (4484.7 euros).

It is important to note that the total PL cost means in the table reflect the average of the reported "total PL cost" from each study rather than the summation of the component averages. Not all reported PL cost items contain the four PL cost components, consequently, such estimate is often an underestimate for the actual total PL resulting from all four components. Table 17 shows the breakdown of the extracted PL cost items along with their annual cost means per patient while figure 18 provides a visual representation of the PL cost averages for musculoskeletal disease from the V4 region.

Table 17. Annual PL costs per patient, means, and standard deviations for the full sample and stratified by country after normalization to reflect 2020-euro value.

Region/Country	PL cost item type	Number of cost items	Mean (SD)
Total Sample			
Visegrád Four (V4)	Absenteeism	6	518.9 (515.2)
	Long-term disability	7	1347.5 (832.6)
	Premature retirement	2	4484.7 (2896.2)
	Short-term disability	4	208.3 (40.5)
	Total PL Cost	6	3724.7 (1707.2)
By country			
Hungary	Absenteeism	3	62.0 (41.6)
	Long-term disability	1	2652.24 (na)
	Premature retirement	2	4484.7 (2896.2)
	Short-term disability	1	238.65 (na)
	Total Cost	3	4015.4 (2505.1)
Poland	Absenteeism	3	975.8 (188.3)
	Long-term disability	6	1130.1 (659.2)
	Short-term disability	3	198.2 (43.0)
	Total PL Cost	3	3434.1 (1347.8)

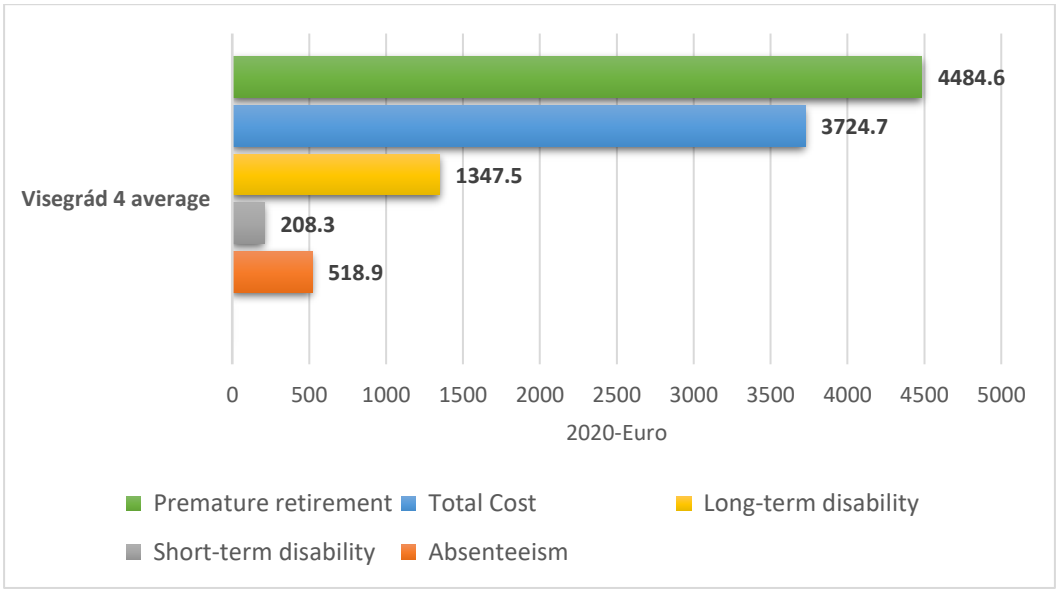


Figure 18. Annual PL cost means per patient for the V4 stratified by PL type.

Although acquiring costs from two countries out of the V4 is a representation limitation, but we did assume that cross-country differences are negligible within the same region (H4). To test that assumption, we used ANOVA to test for significant differences between Hungary and Poland in terms of normalised musculoskeletal disease PL costs. Provided that our dependent variable (2020_cost) showed non-normality indicated by a significant Shapiro–Wilk test value (sig. 0.001) as well as a high skewness value (1.434), in addition to the presence of outliers; we first used logarithmic transformation to adjust our dependent variable (i.e. Log (2020_cost)), we then ran ANOVA to compare cross country PL cost mean differences. Our results indicated an insignificant difference between the country group cost means with an ANOVA significance value of 0.797, which was further confirmed using Brown-Forsythe's non-parametric test (sig. 0.823) provided the violation of equality of variance. Hence, we can confidently assume negligible intercountry differences within the V4 for musculoskeletal disease. Hence, we accept our fourth hypothesis (H4). ANOVA assumptions testing and results are shown in appendix IV.

VIII.2.2.Regional cost adjustments – Tunisia

Table 18 below shows estimated PL cost averages and standard deviations adjusted for Tunisia, using methods 1 through 5 (i.e. M1: calculation of lost productive hours, GDP and HCI adjustment, M3:GDP adjustment alone, M4:International wage adjustment, M5: GDP and Health expenditure). We can see that the highest cost estimates for Tunisia are generated by methods 1 and 4, while methods 3 and 5 gave similar moderate estimates compared to method 2 which gave the lowest estimates overall. By directly comparing the averages (average adjusted to reference average) and provided that our reference value from Tunisia is 324.05 euros per patient per year for absenteeism, it can be apparent that we cannot conclusively decide which method is better by simply comparing the closest absenteeism mean, provided the relatively high SD. Figure 19 provides a visual glimpse into the estimation gap

between the methods for MENA PL means estimation while table 18 shows the estimates by PL type.

Table 18. Tunisia's mean PL cost estimates based on the proposed five methods presented in 2020-euro value.

PL cost item type	PL hours back calculation	GDP+HCI	GDP	Wage ratio	GDP+HE
	Method 1 (SD)	Method 2 (SD)	Method 3 (SD)	Method 4 (SD)	Method 5 (SD)
Absenteeism	644.6 (626.8)	74.3 (72.9)	106.5 (105.8)	529.6 (519.3)	114.8 (116.6)
Short-term disability	300.2 (120.0)	30.4 (6.8)	42.7 (8.3)	217.6 (48.6)	44.1 (20)
Long-term disability	1942.0 (1621.9)	197.1 (128.6)	276.4 (170.3)	1406.7 (920.3)	285.7 (160.2)
Premature retirement	5391.0 (2538.3)	701.1 (452.7)	916.8 (592.1)	5019.2 (3241.4)	815.9 (526.9)
Total PL	4907.4 (1744.8)	558.3 (267.4)	763.0 (349.1)	3989.0 (1915.1)	749.6 (325.4)

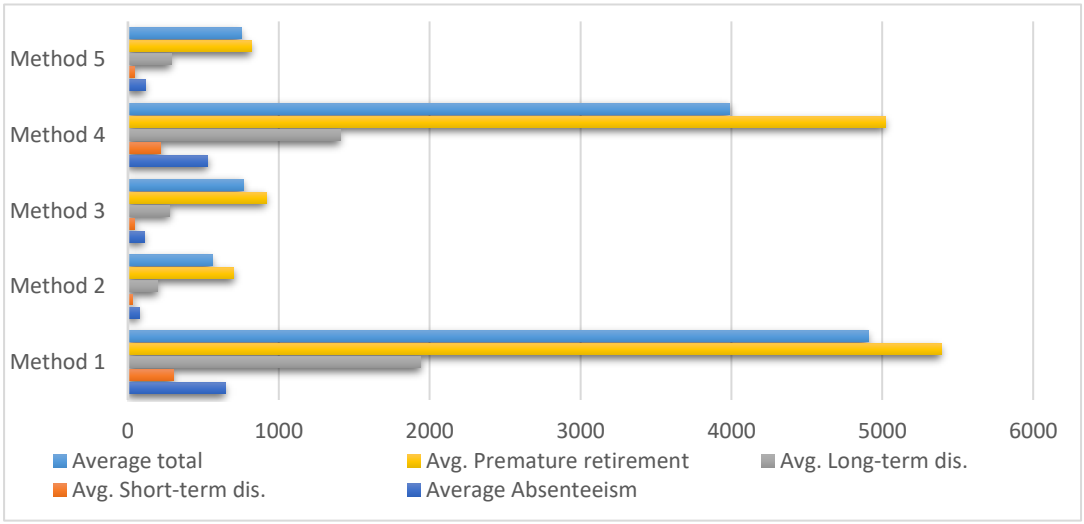


Figure 19. visual representation of PL means cost estimates for Tunisia based on our 5 methods stratified by PL item type.

To test our methodological sensitivities, the MAD was calculated for each cost item individually against our reference value from Tunisia. Provided the PL type specificity of our reference value, we calculated the MAD for absenteeism cost items only (i.e. 6 items). The resulting MADs, their means, and standard error values are recorded in table 19.

Table 19. MAD means and standard error for each method with Tunisia's absenteeism average.

Ref. (324.05)	MAD M1	MAD M2	MAD M3	MAD M4	MAD M5
Absenteeism item 1	292.0	320.7	319.6	299.7	320.1
Absenteeism item 2	1130.3	154.4	79.3	885.0	57.3
Absenteeism item 3	708.3	203.6	150.3	534.2	134.7
Absenteeism item 4	793.2	197.4	141.4	578.5	124.9
Absenteeism item 5	208.8	307.7	302.6	206.8	305.0
Absenteeism item 6	208.0	314.8	311.9	257.6	313.3
Mean	556.8	249.7	217.5	460.3	209.2
Standard Error	**154.9**	**29.8**	**43.2**	**105**	**47.6**

From table 19, It can be seen that GDP-based methods (M2, M3, M5) outperformed wage-based methods (M1, M4) in both precision and accuracy. Our accuracy can be indicated by the lowest MAD, which was acquired using the GDP-adjustment methods; method 5 (μMAD M5= 209.2), followed closely by method 3 and method 2 (μMAD M3= 217.5, μMAD M2= 249.7). On the other hand, precision indicated by the standard error had a different order; method 2 provided the lowest standard error (S.E.= 29.8) followed by method 3 (S.E.= 43.2), then method 5 (S.E.= 47.6). Provided the discrepancy in accuracy among our GDP-based methods, we run paired samples t-test for our GDP-based MADs, to test if the estimated MAD means are significantly different. Paired samples t-test results are presented in Table 20.

Table 20. Paired samples t-test for GDP/capita MADs.

Method	Sig. (2-tailed)	t-statistic	Critical t value (0.05 two-tailed), df=5
MAD M5 - MAD M3	0.120	-1.873	**2.571**
MAD M3 - MAD M2	0.062	-2.397	

Paired samples t-test assumptions were tested and confirmed; each item was an independent cost item coming from an independent study, all cost items used the same measurement method (i.e. HCA), and no outliers were observed. Finally, normality was tested for the difference between the tested MADs using the Shapiro-wilk test provided its appropriateness for normality assessment in small sample sizes (Ghasemi & Zahediasl, 2012). Assumption testing results are presented in appendix IV.

Our paired samples t-test results in table 20 showed non statistically significant means between all of our MAD pairs (M5:M3, M3:M2, and M2:M3) provided the high p-value (p-value > 0.05) in addition to that the calculated t-statistic is below the critical-t cut-off value. Consequently, we accept the null hypothesis (i.e. μn_{ull}: true mean MAD difference = 0) meaning that all our GDP-based adjustment methods provide similar accuracy. Consequently, we can assess our methods based on their precision since they provide similar accuracy. Method 2 (GDP and HCI adjustment) provided the lowest standard error value (S.E.= 29.8) lowering the standard error compared to using method 3 (GDP adjustment alone) (S.E.= 43.2), which gives us evidence to accept our fifth hypothesis (H5) that incorporating HCI with GDP can aid in increasing PL costs transferability. While for method 5 (GDP and HE adjustment), the standard error increased to S.E.=47.6 which indicates lower precision than method 3. Hence, we reject our sixth hypothesis (H6) that incorporating HE with GDP can aid in increasing PL costs transferability precision.

In contrast, wage-based adjustment methods M1 and M4 provided the highest MAD values (µMAD M1= 556.8, µMAD M4= 460.3), as well as standard error estimates (S.E. M1=154.9, S.E. M4= 105) concluding that wage adjustment methods were the least suitable for cross-regional absenteeism PL costs transferability compared to GDP/capita adjustment methods. Figure 20 shows the box plots of our methods MADs for enhanced visual comparability.

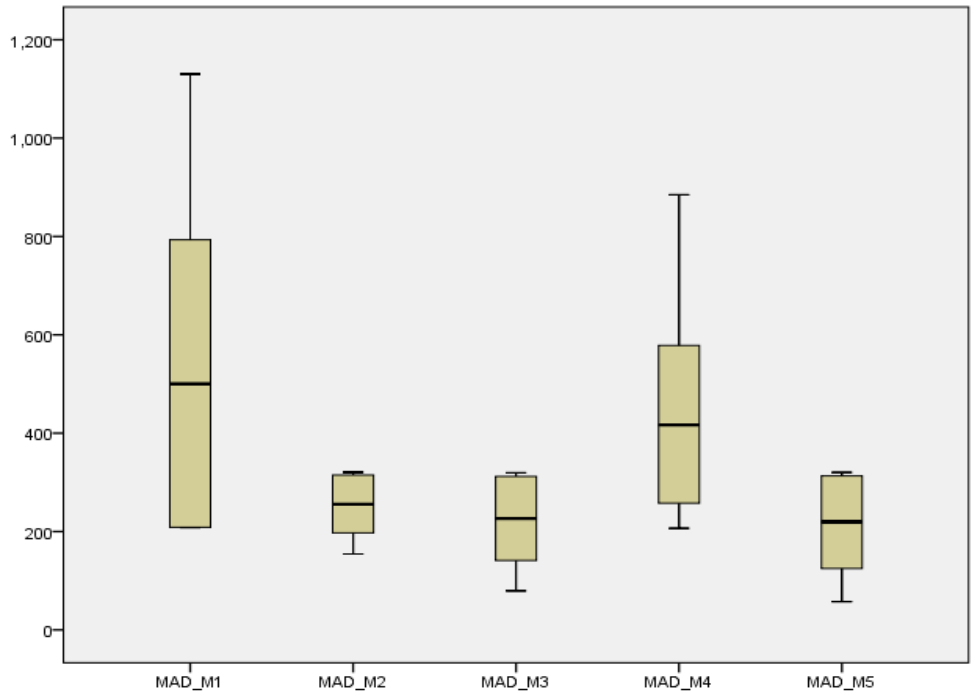


Figure 20. Box plots of absenteeism MADs for each adjustment method. The y-axis represents the cost difference between our methods estimates and Tunisia's reference value.

VIII.3. Discussion

In this chapter, we presented the first regional pooling of indirect costs for musculoskeletal disease from the V4 region, normalised to reflect the value in current euro terms. We confirmed that country differences in normalised PL cost estimates are probably negligible within the same region. Cross-regionally; we demonstrated the superiority of GDP-based adjustments (M2, M3, and M5) compared to wage-based adjustment methods (M1 and M4) in PL costs transferability. We also showed

the usefulness of the HCI (Kraay, 2019) in contributing to the increased precision of transferred PL cost estimates using the GDP-based method. We finally showed that taking the health expenditure as an additional adjustment factor results in an insignificant increase in PL estimates accuracy, at the expense of lowering precision rendering the method's useability limited. Most transferability efforts of health economic evaluations considered one or more of three main aspects; clinical efficacy, resource utilisation, and unit costs (Goeree et al., 2007). In our work, and provided the specificity of human capital productivity, we transferred our PL costs from the V4 into Tunisia by adjusting to reflect for interregional human capital output differences.

Few authors have considered costs pooling to provide an average estimate (Gao et al., 2016; Zhao et al., 2013); we on the other hand, although adopted a similar approach, yet our estimates are specific for one region, mitigating most of the international discrepancy factors that diverge with the geographical, political and economic state. Estimates from a single source proved to be inaccurate or misleading. Pooling of similar methodological results, from a single symmetrical region, for a single disease or disease group, will undoubtedly provide more precise PL cost estimates.

When back calculating PL hours from reported costs (method 1), we based our calculations on that the productive year is 12 months, with a 42-hour working week (168 hours a month). This may have led to an underestimation of the hourly rate given that few, unrepresentative individuals are capable of working for such long hours (Messenger, Lee, & McCann, 2007). Yet, with these underestimations, we still attained the highest positive divergence in MADs among all other methods (lowest accuracy). One may conclude that method 1 may be the least suitable method for interregional transferability of indirect costs. Overall, in wage-based adjustment methods, and although the average wage for our MENA reference was comparable to the V4 average, yet those methods (M1, M4) tended to overestimate the transferred PL costs, concluding that countries with similar average income per capita do not necessarily express similar PL profile. This supports our theory that the specific

human capital output capacity might play a significant role in PL costs transferability. On a relevant note, no caregiver PL costs (replacement/opportunity costs) were reported in our results for musculoskeletal diseases. If wage-based adjustment methods are to be used for caregiver PL costs transferability, results will tend to be even more overestimated unless a modification for the average wage to represent the wage of a caregiver is done.

Our results strongly suggest that the use of HCI adjustment in addition to the GDP/capita adjustment can increase estimates precision, yet this model needs to be replicated for other regions, economies, and diseases with a larger sample size to confirm generalisability. With the current global discrepancy in average human capital output, fine tweaking the transferred PL costs as per the projected national human capital output can provide more precise estimates for policymakers in other parts of the world.

In terms of limitations to our study, it is important to note that our transferability assessment is both limited to absenteeism PL costs and the accuracy of Tunisia's PL estimate. We also did not weigh for disease severity. Moreover, as a result of our -relatively broad- ICD-10 chapter-based pooling, the adjusted PL estimates can be over- or underestimated depending on the specific disease tested within that ICD-10 disease group. Although we aimed to address the population characteristics with the HCI, yet it does not account for individual behavioural characteristics such as patient acceptance, compliance, and incentives.

IX. CONCLUSIONS AND PRACTICAL IMPLICATIONS

Our work has identified several key findings and practical implications for the MENA, V4, and regional PL costs transferability efforts. We found that HTA is a scarcely addressed topic in the MENA region, and any valid efforts in building the field are of great value. Evidence and expertise scarcity are key limiting factors in HTA research growth as demonstrated by the low number of publications and authors in the field. On the other hand, and although the CEE is in better shape, yet the local scientific output comprises less than half of the total regional HTA scientific output, suggesting that international collaborations with more advanced health systems are still fairly active in contributing to knowledge transfer into the CEE region. A similar approach of knowledge sharing can be beneficial to seed HTA efforts in the MENA.

Our MENA scoping review of health economic evaluations identified and categorised the comparative research in the region facilitating future inter- and intraregional HTA collaborations based on mutual interest domains. We saw that NCDs underrepresentation among the region's health economic research was significant, which was probably due to the much larger attention to infectious and respiratory diseases, in light of limited local expertise. We also noticed that the journal rank is not necessarily a good indicator of an evaluation's quality, as sub-standardised evaluations may be published in response to the region's research scarcity. Health economists should pay attention to the accuracy and usability of these results. Funding was a major setback in the region as almost half of the evaluations were either non-funded, or no funding statement was mentioned. Periodic, targeted funding and local capacity building are keys to vitalise the region's health economic base.

Productivity loss significance in social welfare was demonstrated in both regions. Mental and musculoskeletal diseases were the highest consumers of patients' productivity restricting as high as 70% of the patient's economic productive capacity

as shown in our Hungarian NCD patient population. Education and health-related quality of life were of great significance in predicting PL costs, while hospital admissions showed to be the most cost-intensive utility in NCD management. Policies ensuring early started effective treatments, and targeted budget allocations for high PL NCDs are ought to yield significant socioeconomic returns in the medium and long term.

Our updated V4 regional average for musculoskeletal disease PL costs provides a more complete picture of the societal burden of musculoskeletal disease in the V4 region, as close to none of the identified studies reported all patient-related PL cost types (i.e. mortality, absenteeism, presenteeism, early retirement, short and long term disability). Except for presenteeism, a normalised estimate was reported for each type of PL costs separately to be used as a quick-updated guide for policymakers from the V4 in attaining a more complete picture of the monetary impact of musculoskeletal disease PL within their jurisdictions.

For PL costs transferability, health economists are advised to adopt a balanced pooling approach rather than utilising costs from a single study. Furthermore, disregarding the underlying methodological and theoretical aspects of the studies can lead to misinformed policy decisions. Ensuring that the pooling is done for similar methodological studies is crucial in attaining precise PL estimates. Moreover, and provided the significant global discrepancies in average human capital output, fine tweaking the transferred PL costs as per the projected national human capital output can provide more precise estimates for policymakers in other parts of the world. Adjusting for GDP and HCI combined, can significantly contribute to increasing the precision of transferred PL estimates.

X. OWN PUBLICATIONS RELATED TO THIS DISSERTATION

X.1. Journal papers

Rashdan, O., & Brodszky, V. (2020). Productivity Loss in Patients With Chronic Diseases: A Pooled Economic Analysis of Hungarian Cost-of-Illness Studies. Value in Health Regional Issues, 22, 75-82.

Zrubka, Z., **Rashdan, O.**, & Gulácsi, L. (2020). Health economic publications from the Middle East and North Africa Region: a scoping review of the volume and methods of research. Global Journal on Quality and Safety in Healthcare, 3(2), 44-54.

X.2. Conference papers, abstracts and presentations

Rashdan, O., & Alshafeey, M. (2019). HTA in CEE Countries: A Bibliometric Analysis of Research. In Proceedings of FIKUSZ Symposium for Young Researchers (pp. 192-203). Óbuda University Keleti Károly, Faculty of Economics.

X.3. Conference abstracts and poster presentations

Rashdan, O. & Brodszky, V. (2019). PP38 Productivity Loss In Patients With Chronic Diseases: A Pooled Analysis. International Journal of Technology Assessment in Health Care, 35(S1), 44-44.

Rashdan, O., Zrubka, Z., & Gulácsi, L. (2020). PMU10 A Scoping Review Of Health Economic Evaluations From The Middle East And North Africa Region. Value in Health, 23, S234-S235.

Rashdan, O., Brodszky, V., Péntek, M., Gulácsi, L., & Zrubka, Z. (2020). PNS32 Towards a Healthcare Cost Catalogue for Middle EAST and North Africa: A Systematic Review of Productivity Loss Costs Reported in Health Economic Publications between 1989-2019. Value in Health, 23, S649.

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APPENDIX I

- Supplementary table 1. search results for CEE HTA research - chapter IV

#	Authors	Article title	Publication year	Journal name	Number of citations	DOI	SJR
1	Baran-Kooiker A., Atikeler K., Gaitova K., Holownia-Voloskova M., Turcu-Stiolica A., Kooiker C., Piniazhko O., Czech M.	Applicability of the EVIDEM multi-criteria decision analysis framework for orphan drugs Ñ results from a study in 7 Eurasian countries	2018	Acta Poloniae Pharmaceutica	0	10.32383/appdr/102681	Q3
2	Kleijnen S., Lipska I., Leonardo Alves T., Meijboom K., Elsada A., Vervölgyi V., d'Andon A., Timoney A., Leufkens H.G., De Boer A., Goettsch W.G.	Relative effectiveness assessments of oncology medicines for pricing and reimbursement decisions in European countries	2016	Annals of Oncology	13	10.1093/annonc/mdw233	Q1
3	Jakubczyk M., Kamiński B.	Fuzzy approach to decision analysis with multiple criteria and uncertainty in health technology assessment	2017	Annals of Operations Research	7	10.1007/s10479-015-1910-9	Q1
4	Svedbom A., Hernlund E., Ivergård M., Compston J., Cooper C., Stenmark J., McCloskey E.V., Jönsson B., Kanis J.A.	Osteoporosis in the European Union: A compendium of country-specific reports	2013	Archives of Osteoporosis	261	10.1007/s11657-013-0137-0	Q2
5	Iskrov G., Stefanov R.	Criteria for drug reimbursement decision-making: An emerging public health challenge in Bulgaria	2016	Balkan Medical Journal	6	10.5152/balkanmedj.2015.15185	Q3
6	Detiček A., Janzic A., Locatelli I., Kos M.	Decision-making criteria for medicine reimbursement in Slovenia: An expert panel discussion	2018	BMC Health Services Research	0	10.1186/s12913-018-3299-z	Q1
7	Inotai A., Pékli M., Jóna G., Nagy O., Remák E., Kaló Z.	Attempt to increase the transparency of fourth hurdle implementation in Central-Eastern European middle income countries: Publication of the critical appraisal methodology	2012	BMC Health Services Research	14	10.1186/1472-6963-12-332	Q1

8	Angelis A., Lange A., Kanavos P.	Using health technology assessment to assess the value of new medicines: results of a systematic review and expert consultation across eight European countries	2018	European Journal of Health Economics	23	10.1007/s10198-017-0871-0	Q1
9	Gulácsi L., Rotar A.M., Niewada M., Löblová O., Rencz F., Petrova G., Boncz I., Klazinga N.S.	Health technology assessment in Poland, the Czech Republic, Hungary, Romania and Bulgaria	2014	European Journal of Health Economics	43	10.1007/s10198-014-0590-8	Q1
10	Horváth Cs.Z., Sebestyén A., Österle A., Endrei D., Betlehem J., Oláh A., Imre L., Bagosi G., Boncz I.	Economic burden of long-term care of rheumatoid arthritis patients in Hungary	2014	European Journal of Health Economics	6	10.1007/s10198-014-0601-9	Q1
11	Kozierkiewicz A., Trąbka W., Romaszewski A., Gajda K., Gilewski D.	Definition of the "health benefit basket" in Poland	2005	European Journal of Health Economics	6	10.1007/s10198-005-0320-3	Q2
12	Ivlev I., Vacek J., Kneppo P.	Multi-criteria decision analysis for supporting the selection of medical devices under uncertainty	2015	European Journal of Operational Research	29	10.1016/j.ejor.2015.05.075	Q1
13	Vassileva M., Kamusheva M., Manova M., Savova A., Tachkov K., Petrova G.	Historical overview of regulatory framework development on pricing and reimbursement of medicines in Bulgaria	2018	Expert Review of Pharmacoeconomics and Outcomes Research	0	10.1080/14737167.2019.1592680	Q2
14	Kawalec P., Malinowski K.P., Trąbka W.	Trends and determinants in reimbursement decision-making in Poland in the years 2013–2015	2018	Expert Review of Pharmacoeconomics and Outcomes Research	1	10.1080/14737167.2018.1384696	Q2
15	Bochenek T., Kocot E., Rodzinka M., Godman B., Maciejewska K., Kamal S., Pilc A.	The transparency of published health technology assessment-based recommendations on pharmaceutical reimbursement in Poland	2017	Expert Review of Pharmacoeconomics and Outcomes Research	4	10.1080/14737167.2017.1262767	Q2
16	Neumann D., Jabłecka A.	Reimbursement of biosimilars in Poland: is there a link to health technology assessment?	2016	Expert Review of Pharmacoeconomics and Outcomes Research	1	10.1586/14737167.2016.1141051	Q2
17	Paveliu S., Radu C.-P., Tudose F., Tudose C., Arsene A.L.	Cost-effectiveness-analysis and the concept of quality adjusted life year (qaly) in Romania	2011	Farmacia	4	N/A	Q2
18	Iskrov G.G., Raycheva R.D., Stefanov R.S.	Insight into reimbursement decision-making criteria in	2013	Folia medica	12	N/A	Q3

		Bulgaria: implications for orphan drugs.					
19	Malinowski K.P., Kawalec P., Trabka W., Sowada C., Pilc A.	Reimbursement of orphan drugs in Europe in relation to the type of authorization by the European medicines agency and the decision making based on health technology assessment	2018	Frontiers in Pharmacology	1	10.3389/fphar.2018.01263	Q1
20	Kawalec P., Tesar T., Vostalova L., Draganic P., Manova M., Savova A., Petrova G., Rugaja Z., Männik A., Sowada C., Stawowczyk E., Harsanyi A., Inotai A., Turcu-Stiolica A., Gulbinovic J., Pilc A.	Pharmaceutical regulation in Central and Eastern European countries: A current review	2017	Frontiers in Pharmacology	5	10.3389/fphar.2017.00892	Q1
21	Iskrov G., Miteva-Katrandzhieva T., Stefanov R.	Multi-criteria decision analysis for assessment and appraisal of orphan drugs	2016	Frontiers in Public Health	13	10.3389/FPUBH.2016.00214	Q2
22	Roediger A., Freischem B., Reiland J.-B.	What pricing and reimbursement policies to use for off-patent biologicals in Europe? - Results from the second EBE biological medicines policy survey	2017	GaBI Journal	4	10.5639/gabij.2017.0602.014	Q1
23	Acha V., Allin P., Bergunde S., Bisordi F., Roediger A.	What pricing and reimbursement policies to use for off-patent biologicals? - Results from the EBE 2014 biological medicines policy survey	2015	GaBI Journal	10	10.5639/gabij.2015.0401.006	Q1
24	Ozierański P., Löblová O., Nicholls N., Csanádi M., Kaló Z., McKee M., King L.	Transparency in practice: Evidence from 'verification analyses' issued by the Polish Agency for Health Technology Assessment in 2012-2015	2018	Health Economics, Policy and Law	3	10.1017/S1744133117000342	Q1
25	Csanádi M., Löblová O., Ozierański P., Harsányi A., Kaló Z., McKee M., King L.	When health technology assessment is confidential and experts have no power: The case of Hungary	2018	Health Economics, Policy and Law	9	10.1017/S1744133118000051	Q1
26	Löblová O.	Who's afraid of institutionalizing health technology assessment (HTA)?: Interests and policy	2018	Health Economics, Policy and Law	3	10.1017/S174413311700024X	Q1

		positions on HTA in the Czech Republic					
27	Kiselova Bilekova B., Gavurova B., Rogalewicz V.	Application of the HTA Core Model for complex evaluation of the effectiveness and quality of Radium-223 treatment in patients with metastatic castration resistant prostate cancer	2018	Health Economics Review	0	10.1186/s13561-018-0211-9	Q2
28	Augustynowicz A., Czerw A., Borowska M., Deptała A., Dykowska G., Fronczak A.	Prevention of overweight and obesity undertaken by local government units in Poland	2018	Health Policy	0	10.1016/j.healthpol.2019.03.006	Q1
29	Wranik W.D., Zielińska D.A., Gambold L., Sevgur S.	Threats to the value of Health Technology Assessment: Qualitative evidence from Canada and Poland	2018	Health Policy	1	10.1016/j.healthpol.2018.12.001	Q1
30	Maynou L., Cairns J.	What is driving HTA decision-making? Evidence from cancer drug reimbursement decisions from 6 European countries	2018	Health Policy	2	10.1016/j.healthpol.2018.11.003	Q1
31	Csanádi M., Ozierański P., Löblová O., King L., Kaló Z., Botz L.	Shedding light on the HTA consultancy market: Insights from Poland	2018	Health Policy	0	10.1016/j.healthpol.2019.08.008	Q1
32	Malinowski K.P., Kawalec P., Trąbka W.	Impact of patient outcomes and cost aspects on reimbursement recommendations in Poland in 2012–2014	2016	Health Policy	6	10.1016/j.healthpol.2016.09.016	Q1
33	Kawalec P., Malinowski K.P.	Relating Health Technology Assessment recommendations and reimbursement decisions in Poland in years 2012–2014, a retrospective analysis	2016	Health Policy	9	10.1016/j.healthpol.2016.09.021	Q1
34	Lopert R., Ruiz F., Chalkidou K.	Applying rapid 'de-facto' HTA in resource-limited settings: Experience from Romania	2013	Health Policy	14	10.1016/j.healthpol.2013.07.019	Q1
35	Ozieranski P., McKee M., King L.	The politics of health technology assessment in Poland	2012	Health Policy	21	10.1016/j.healthpol.2012.10.001	Q1
36	Iskrov G., Miteva-Katrandzhieva T., Stefanov R.	Challenges to orphan drugs access in Eastern Europe: The case of Bulgaria	2012	Health Policy	21	10.1016/j.healthpol.2012.08.013	Q1

37	Kolasa K., Schubert S., Manca A., Hermanowski T.	A review of Health Technology Assessment (HTA) recommendations for drug therapies issued between 2007 and 2009 and their impact on policymaking processes in Poland	2011	Health Policy	22	10.1016/j.healthpol.2011.05.001	Q1
38	Gibis B., Artiles J., Corabian P., Meiesaar K., Koppel A., Jacobs P., Serrano P., Menon D.	Application of strengths, weaknesses, opportunities and threats analysis in the development of a health technology assessment program	2001	Health Policy	19	10.1016/S0168-8510(01)00149-X	Q1
39	Vokó Z., Cheung K.L., Józwiak-Hagymásy J., Wolfenstetter S., Jones T., Muñoz C., Evers S.M.A.A., Hiligsmann M., de Vries H., Pokhrel S.	Similarities and differences between stakeholders' opinions on using Health Technology Assessment (HTA) information across five European countries: Results from the EQUIPT survey	2016	Health Research Policy and Systems	11	10.1186/s12961-016-0110-7	Q1
40	Sprigg N., Flaherty K., Appleton J.P., Al-Shahi Salman R., Bereczki D., Beridze M., Ciccone A., Collins R., Dineen R.A., Duley L., Egea-Guerrero J.J., England T.J., Karlinski M., Krishnan K., Laska A.C., Law Z.K., Ovesen C., Ozturk S., Pocock S.J., Roberts I., Robinson T.G., Roffe C., Peters N., Scutt P., Thanabalan J., Werring D., Whynes D., Woodhouse L., Bath P.M.	Tranexamic acid to improve functional status in adults with spontaneous intracerebral haemorrhage: the TICH-2 RCT	2018	Health technology assessment	0	10.3310/hta23350	Q1
41	Brereton L., Wahlster P., Mozygemba K., Lysdahl K.B., Burns J., Polus S., Tummers M., Refolo P., Sacchini D., Leppert W., Chilcott J., Ingleton C., Gardiner C., Goyder E.	Stakeholder involvement throughout health technology assessment: An example from palliative care	2017	International Journal of Technology Assessment in Health Care	4	10.1017/S026646231700068X	Q2
42	Polus S., Pfadenhauer L., Brereton L., Leppert W., Wahlster P., Gerhardus A., Rehfuess E.	A consultation guide for assessing the applicability of health technologies: A case study	2017	International Journal of Technology Assessment in Health Care	2	10.1017/S0266462317000745	Q2

43	Benisheva-Dimitrova T., Sidjimova D., Cherneva D., Kralimarkov N.	PRICING, REIMBURSEMENT, and HEALTH TECHNOLOGY ASSESSMENT of MEDICINAL PRODUCTS in BULGARIA	2017	International Journal of Technology Assessment in Health Care	1	10.1017/S0266462317000551	Q2
44	Huic M., Tandara Hacek R., Svajger I.	HEALTH TECHNOLOGY ASSESSMENT in CENTRAL, EASTERN, and SOUTH EUROPEAN COUNTRIES: CROATIA	2017	International Journal of Technology Assessment in Health Care	1	10.1017/S026646231700054X	Q2
45	Lipska I., McAuslane N., Leufkens H., Hövels A.	A DECADE of HEALTH TECHNOLOGY ASSESSMENT in POLAND	2017	International Journal of Technology Assessment in Health Care	1	10.1017/S0266462317000563	Q2
46	Atanasijevic D., Zah V.	HEALTH TECHNOLOGY ASSESSMENT in SERBIA	2017	International Journal of Technology Assessment in Health Care	0	10.1017/S0266462317000538	Q2
47	Scintee S.G., Ciutan M.	DEVELOPMENT of HEALTH TECHNOLOGY ASSESSMENT in ROMANIA	2017	International Journal of Technology Assessment in Health Care	0	10.1017/S0266462317000095	Q2
48	Tesar T., Hloska A., Wawruch M., Lehocka L., Snopkova M., Masarykova L.	INTRODUCTION of HEALTH TECHNOLOGY ASSESSMENT for MEDICINES in SLOVAKIA	2017	International Journal of Technology Assessment in Health Care	4	10.1017/S026646231700006X	Q2
49	Vostalová L., Mazelová J., Samek J., Vocelka M.	HEALTH TECHNOLOGY ASSESSMENT in EVALUATION of PHARMACEUTICALS in the CZECH REPUBLIC	2017	International Journal of Technology Assessment in Health Care	1	10.1017/S0266462317000204	Q2
50	Prevolnik Rupel V.	CURRENT IMPLEMENTATION of HEALTH TECHNOLOGY ASSESSMENT in HEALTHCARE SYSTEM in SLOVENIA	2017	International Journal of Technology Assessment in Health Care	1	10.1017/S0266462317000083	Q2
51	Garau M., Shah K.K., Sharma P., Towse A.	IS the LINK between HEALTH and WEALTH CONSIDERED in DECISION MAKING? RESULTS from A QUALITATIVE STUDY	2016	International Journal of Technology Assessment in Health Care	1	10.1017/S0266462315000616	Q2
52	Kolasa K., Wasiak R.	Health technology assessment in Poland and Scotland: Comparison of process and decisions	2012	International Journal of Technology Assessment in Health Care	12	10.1017/S0266462311000699	Q1

53	Kolasa K., Dziomdziora M., Fajutrao L.	What aspects of the health technology assessment process recommended by international health technology assessment agencies received the most attention in Poland in 2008?	2011	International Journal of Technology Assessment in Health Care	6	10.1017/S0266462310001236	Q1
54	Noorani H.Z., Husereau D.R., Boudreau R., Skidmore B.	Priority setting for health technology assessments: A systematic review of current practical approaches	2007	International Journal of Technology Assessment in Health Care	79	10.1017/S026646230707050X	Q1
55	Corabian P., Hailey D., Harstall C., Juzwishin D., Moga C.	Mentoring a developing health technology assessment initiative in Romania: An example for countries with limited experience of assessing health technology	2005	International Journal of Technology Assessment in Health Care	7	10.1017/S0266462305050737	Q2
56	Gulácsi L., Boncz I., Drummond M.	Issues for countries considering introducing the "fourth hurdle": The case of Hungary	2004	International Journal of Technology Assessment in Health Care	33	10.1017/S0266462304001151	Q1
57	[No author name available]	Report from the Hungarian Coordinating Office for Health Technology Assessment (Hcohta)	1999	International Journal of Technology Assessment in Health Care	1	10.1017/S0266462300005316	Q1
58	Donin G., Barták M., Kneppo P.	Estimation of medical equipment prices–a case study of tomotherapy equipment in the Czech Republic	2017	Journal of Business Economics and Management	1	10.3846/16111699.2017.1409798	Q2
59	Caro Martínez A., Espín Balbino J., Lemgruber A., Martín Ruiz E., Olry De Labry Lima A., Garciá-Mochón L., Lessa F.	Adoption of the HPV vaccine: A case study of three emerging countries	2017	Journal of Comparative Effectiveness Research	1	10.2217/cer-2016-0071	Q2
60	Martín-Ruiz E., Balbino J.E., Lemgruber A., Caro-Martínez A., Lessa F., Olry-De-Labry-Lima A., Pérez-Velasco R., García-Mochón L.	Adoption of trastuzumab for breast cancer in four emerging countries in the use of health technology assessment: A case study	2016	Journal of Comparative Effectiveness Research	1	10.2217/cer-2015-0025	Q2
61	Brogan A.P., DeMuro C., Barrett A.M., D'Alessio D., Bal V., Hogue S.L.	Payer perspectives on patient-reported outcomes in health care decision making: Oncology examples	2017	Journal of Managed Care & Specialty Pharmacy	11	10.18553/jmcp.2017.23.2.125	Q1
62	Rosina J., Rogalewicz V., Ivlev I., Juřičková I., Donin G., Jantosová	Health technology assessment for medical devices	2014	Lekar a Technika	14	N/A	Q4

	N., Vacek J., Otawová R., Kneppo P.						
63	Kolasa K., Zwolinski K.M., Zah V., Kaló Z., Lewandowski T.	Revealed preferences towards the appraisal of orphan drugs in Poland - Multi criteria decision analysis	2018	Orphanet Journal of Rare Diseases	1	N/A	Q1
64	Kawalec P., Sagan A., Pilc A.	The correlation between HTA recommendations and reimbursement status of orphan drugs in Europe	2016	Orphanet Journal of Rare Diseases	10	10.1186/s13023-016-0501-4	Q1
65	Kolasa K., Zwolinski K.M., Kalo Z., Hermanowski T.	Potential impact of the implementation of multiple-criteria decision analysis (MCDA) on the Polish pricing and reimbursement process of orphan drugs	2016	Orphanet Journal of Rare Diseases	23	10.1186/s13023-016-0388-0	Q1
66	Radziszewski M., Kozłowski P.	Predicting functional outcomes in patients with femoral neck fractures treated by hemiarthroplasty [Prognozowanie czynnościowego wyniku leczenia operacyjnego pacjentów ze złamaniami szyjki kości udowej prowadzonego z użyciem protezy połowiczej stawu biodrowego]	2017	Ortopedia Traumatologia Rehabilitacja	1	10.5604/01.3001.0010.4643	Q3
67	Brereton L., Ingleton C., Gardiner C., Goyder E., Mozygemba K., Lysdahl K.B., Tummers M., Sacchini D., Leppert W., Blažević ienė A., Van Der Wilt G.J., Refolo P., De Nicola M., Chilcott J., Oortwijn W.	Lay and professional stakeholder involvement in scoping palliative care issues: Methods used in seven European countries	2017	Palliative Medicine	8	10.1177/0269216316649154	Q1
68	EUnetHTA Joint Action 2, Work Package 7, Subgroup 3, Heintz E., Gerber-Grote A., Ghabri S., Hamers F.F., Rupel V.P., Slabe-Erker R., Davidson T.	Is There a European View on Health Economic Evaluations? Results from a Synopsis of Methodological Guidelines Used in the EUnetHTA Partner Countries	2016	PharmacoEconomics	26	10.1007/s40273-015-0328-1	Q1

69	Löblová O.	When Epistemic Communities Fail: Exploring the Mechanism of Policy Influence	2018	Policy Studies Journal	7	10.1111/psj.12213	Q1
70	Kolasa K., Turlej A., Hermanowski T.	Health technology assessment of public health programmes in Poland, years 2010 and 2013	2016	Przeglad Epidemiologiczny	0	N/A	Q3
71	Wilk N., Wierzbicka N., Skrzekowska-Baran I., Moćko P., Tomassy J., Kloc K.	Study types and reliability of Real World Evidence compared with experimental evidence used in Polish reimbursement decision-making processes	2017	Public Health	1	10.1016/j.puhe.2016.12.025	Q2
72	Kleijnen S., Leonardo Alves T., Meijboom K., Lipska I., De Boer A., Leufkens H.G., Goettsch W.G.	The impact of quality-of-life data in relative effectiveness assessments of new anti-cancer drugs in European countries	2017	Quality of Life Research	1	10.1007/s11136-017-1574-9	Q1
73	Damian S., Necula R., Sandu A., Iliescu M.L., Ioan B.	Ethical evaluation model for technologies. the role of medical technology in the development of autonomy in diabetes patient.	2013	Revista medico-chirurgicală a Societăţii de Medici şi Naturalişti din Iaşi	2	N/A	Q4
74	Inotai A., Rojkovich B., Fülöp A., Jászay E., Ágh T., Mészáros A.	Health-related quality of life and utility in patients receiving biological and non-biological treatments in rheumatoid arthritis	2012	Rheumatology International	13	10.1007/s00296-010-1721-x	Q2
75	Kurowska P., Królak A., Giermaziak W.	Health policy programs realised in Poland in 2016-2017	2018	Roczniki Panstwowego Zakladu Higieny	0	N/A	Q3
76	Hevér N., Balogh O.	The German approach to cost-effectiveness analysis in health care	2013	Society and Economy	1	10.1556/SocEc.2013.0008	Q2
77	Orlewska E.	Challenges and changes in the Polish healthcare system	2011	Society and Economy	3	10.1556/SocEc.33.2011.3.8	Q4
78	Neugebauer E.A.M., Becker M., Buess G.F., Cuschieri A., Dauben H.-P., Fingerhut A., Fuchs K.H., Habermalz B., Lantsberg L., Morino M., Reiter-Theil S., Soskuty G., Wayand W., Welsch T.	EAES recommendations on methodology of innovation management in endoscopic surgery	2010	Surgical Endoscopy	35	10.1007/s00464-009-0818-3	Q1
79	Mihajlović J., Hovius J.W.R., Sprong H., Bogovič P., Postma M.J., Strle F.	Cost-effectiveness of a potential anti-tick vaccine with combined protection against Lyme	2018	Ticks and Tick-borne Diseases	1	10.1016/j.ttbdis.2018.08.014	Q1

		borreliosis and tick-borne encephalitis in Slovenia					
80	Akehurst R.L., Abadie E., Renaudin N., Sarkozy F.	Variation in Health Technology Assessment and Reimbursement Processes in Europe	2017	Value in Health	17	10.1016/j.jval.2016.08.725	Q1
81	Djambazov S.N., Giammanco M.D., Gitto L.	Factors That Predict Overall Patient Satisfaction With Oncology Hospital Care in Bulgaria	2018	Value in Health Regional Issues	0	10.1016/j.vhri.2018.11.006	Q2
82	Beletsi A., Koutrafouri V., Karampli E., Pavi E.	Comparing Use of Health Technology Assessment in Pharmaceutical Policy among Earlier and More Recent Adopters in the European Union	2018	Value in Health Regional Issues	1	10.1016/j.vhri.2018.08.002	Q2
83	Radu C.-P., Pana B.C., Furtunescu F.L.	Drug Policy in Romania	2018	Value in Health Regional Issues	2	10.1016/j.vhri.2017.11.003	Q2
84	Skoupá J.	Drug Policy—The Czech Republic	2017	Value in Health Regional Issues	5	10.1016/j.vhri.2017.08.002	Q2
85	Dimova A., Rohova M., Atanasova E., Kawalec P., Czok K.	Drug Policy in Bulgaria	2017	Value in Health Regional Issues	3	10.1016/j.vhri.2017.08.001	Q2
86	Culig J., Antolic S., Szkultecka-Dębek M.	Drug Policy—Croatia	2017	Value in Health Regional Issues	4	10.1016/j.vhri.2017.07.005	Q2
87	Jahnz-Różyk K., Kawalec P., Malinowski K., Czok K.	Drug Policy in Poland	2017	Value in Health Regional Issues	7	10.1016/j.vhri.2017.07.001	Q2
88	Inotai A., Csanádi M., Harsányi A., Németh B.	Drug Policy in Central Eastern Europe—Hungary	2017	Value in Health Regional Issues	5	10.1016/j.vhri.2017.06.003	Q2
89	Radu C.-P., Chiriac N.D., Pravat A.M.	The Development of the Romanian Scorecard HTA System	2016	Value in Health Regional Issues	5	10.1016/j.vhri.2016.07.006	Q2
90	Jakubiak-Lasocka J., Jakubczyk M.	Cost-effectiveness versus Cost-Utility Analyses: What Are the Motives Behind Using Each and How Do Their Results Differ?-A Polish Example	2014	Value in Health Regional Issues	19	10.1016/j.vhri.2014.06.008	Q3
91	Skoupá J., Annemans L., Hájek P.	Health economic data requirements and availability in the European Union: Results of a survey among 10 European countries	2014	Value in Health Regional Issues	11	10.1016/j.vhri.2014.06.003	Q3

92	Kaló Z., Bodrogi J., Boncz I., Dózsa C., Jóna G., Kövi R., Pásztélyi Z., Sinkovits B.	Capacity building for HTA implementation in middle-income countries: The case of hungary	2013	Value in Health Regional Issues	34	10.1016/j.vhri.2013.06.002	Q3
93	Niewada M., Polkowska M., Jakubczyk M., Golicki D.	What influences recommendations issued by the agency for health technology assessment in Poland? A glimpse into decision makers' preferences	2013	Value in Health Regional Issues	10	10.1016/j.vhri.2013.05.002	Q3
94	Rupel V.P., Ogorevc M.	The EQ-5D health states value set for Slovenia	2012	Zdravstveno Varstvo	11	10.2478/v10152-012-0015-y	Q4

- Supplementary table 2. search results for MENA HTA research - chapter IV

Authors	Title	Year	Source title	Cited by	DOI	Exclusion/inclusion
Leadley R.M., Lang S., Misso K., Bekkering T., Ross J., Akiyama T., Fietz M., Giugliani R., Hendriksz C.J., Hock N.L., McGill J., Olaye A., Jain M., Kleijnen J.	A systematic review of the prevalence of Morquio A syndrome: challenges for study reporting in rare diseases	2014	Orphanet journal of rare diseases	40	10.1186/s13023-014-0173-x	out of topic scope
Thomas J.A., Iliescu V., Crawford D.H., Ellouz R., Cammoun M., De-Thé G.	Expression of HLA-DR antigens in nasopharyngeal carcinoma: An immunohistological analysis of the tumour cells and infiltrating lymphocytes	1984	International Journal of Cancer	36	10.1002/ijc.2910330616	out of topic scope
Mehri S., Mahjoub S., Hammami S., Zaroui A., Frih A., Betbout F., Mechmeche R., Hammami M.	Renin-Angiotensin system polymorphisms in relation to hypertension status and obesity in a Tunisian population	2012	Molecular Biology Reports	30	10.1007/s11033-011-1187-2	out of topic scope
Perron L., Senikas V., Burnett M., Davis V., Aggarwal A., Bernardin J., Clark V., Davis V., Fisher W., Pellizzari R., Polomeno V., Rutherford M., Sabourin J., Shapiro J., Akhtar S., Camire B., Christilaw J., Corey J., Nelson E., Pierce M., Robertson D., Simmonds A.	Female Genital Cutting	2013	Journal of Obstetrics and Gynaecology Canada	25	10.1016/S1701-2163(15)30792-1	out of geographical scope
Elsisi G.H., Kaló Z., Eldessouki R., Elmahdawy M.D., Saad A., Ragab S., Elshalakani A.M., Abaza S.	Recommendations for reporting pharmacoeconomic evaluations in Egypt	2013	Value in Health Regional Issues	19	10.1016/j.vhri.2013.06.014	Included
Babigumira J.B., Jenny A.M., Bartlein R., Stergachis A., Garrison L.P.	Health technology assessment in low- and middle-income countries: A landscape assessment	2016	Journal of Pharmaceutical Health Services Research	14	10.1111/jphs.12120	Included
Kabadou I.A., Soualmia H., Jemaa R., Feki M., Kallel A., Souheil O., Taieb S.H., Sanhaji H., Kaabachi N.	G protein β3 subunit gene C825T and angiotensin converting enzyme gene insertion/deletion polymorphisms in hypertensive Tunisian population	2013	Clinical Laboratory	8	10.7754/Clin.Lab.2013.111105	out of topic scope

Elbarazi I., Devlin N.J., Katsaiti M.-S., Papadimitropoulos E.A., Shah K.K., Blair I.	The effect of religion on the perception of health states among adults in the United Arab Emirates: A qualitative study	2017	BMJ Open	4	10.1136/bmjopen-2017-016969	out of topic scope
Hayajneh W.A., Daniels V.J., James C.K., Kanibir M.N., Pilsbury M., Marks M., Goveia M.G., Elbasha E.H., Dasbach E., Acosta C.J.	Public health impact and cost effectiveness of routine childhood vaccination for hepatitis a in Jordan: A dynamic model approach	2018	BMC Infectious Diseases	2	10.1186/s12879-018-3034-8	Included
Darawsheh B., Germeni E.	Implementing health technology assessment in Kuwait: A qualitative study of perceived barriers and facilitators	2019	International Journal of Technology Assessment in Health Care	1	10.1017/S0266462319000710	Included
Bennaceur M., Belabidi F., Riche M., Otmani F., Arrada M.	P-070: Hypertension and cancer: a mysterious association! [HTA et cancer : une association mystérieuse !]	2015	Annales de Cardiologie et d'Angeiologie	0	10.1016/S0003-3928(16)30114-7	French language
Kharoubi O., Benglia A.	P-076: Chronic renal failure and parathyroid hormone [Insuffisance rénale chronique et parathormone]	2015	Annales de Cardiologie et d'Angeiologie	0	10.1016/S0003-3928(16)30120-2	French language
Belhadj N., Lahmer A., Brouri M.	P-125: Prevalence of lomer limb arteriopathy obliterans in the town hypertensif of Sidi Bel-Abbès [Prévalence de l'artériopathie oblitérante des membres inférieurs chez les sujets hypertendus dans la commune de Sidi Bel-Abbès]	2015	Annales de Cardiologie et d'Angeiologie	0	10.1016/S0003-3928(16)30169-X	French language
Fennira E., Chaari C., Abdessleme H., Hamdi S., Mhidhi S., Harrabi T., Bettaieb J., Tertek H., Ben Mami F.	P-065: Frequency, risk factors and evolution of pre-eclampsia in a population of tunisian diabetic women [Fréquence, facteurs de risque et évolution de la toxémie gravidique chez une population de femmes diabétiques tunisiennes]	2015	Annales de Cardiologie et d'Angeiologie	0	10.1016/S0003-3928(16)30109-3	French language
Mahnane A., Abdoun M., Bouaoud S., Zaidi Z., Hamdi-Cherif M., Lafi N.	P-129: Epidemiology hospital mortality by disease cardiovascular (HTA) in Setif, 2006–2014 [Épidémiologie de la mortalité hospitalière par maladie cardiovasculaire (HTA) à Sét if, 2006–2014]	2015	Annales de Cardiologie et d'Angeiologie	0	10.1016/S0003-3928(16)30173-1	French language
Batouche D., Elhalimi K., Chaib N., Abassini S., Touhami Y., Negadi M.A., Mentouri Z.	P-090: The autonomic disorders and high blood pressure during Guillain Barre syndrome in children crossed University Hospital Center in Oran [La dysautonomie neurovégétative et l'hypertension artérielle au cours du syndrome de Guillain Barré chez les enfants au CHU d'Oran]	2015	Annales de Cardiologie et d'Angeiologie	0	10.1016/S0003-3928(16)30134-2	French language

Saada F., Talbi S., Atrouz F., Ouanoughi S.	P-188: Blood pressure control in primary glomerulonephritis: about 153 cases [Contrôle de la pression artérielle au cours des néphropathies glomérulaires primitives : à propos de 153 cas]	2015	Annales de Cardiologie et d'Angeiologie	0	10.1016/S0003-3928(16)30231-1	French language
Moussaoui F., Bali Tabet R., Kherbouche M., Meziane Tani A.	P-142: HTA main risk factor of heart failure at the University Hospital of Tlemcen? A series of 206 patients	2015	Annales de Cardiologie et d'Angeiologie	0	10.1016/S0003-3928(16)30185-8	French language
Zelmat S., Mazour F., atouche D.D.	P-053: Incidence of prematurity in the HELLP Syndrome [Incidence de la prématurité dans le HELLP Syndrome]	2015	Annales de Cardiologie et d'Angeiologie	0	10.1016/S0003-3928(16)30097-X	French language
Marouani M., Gharmoul M., Ahmed S., Khlifi A., Khairi H.	P-042: Severe preeclampsia: about 53 cases [Pré-éclampsie sévère : à propos de 53 cas]	2015	Annales de Cardiologie et d'Angeiologie	0	10.1016/S0003-3928(16)30086-5	French language
Bachir Cherif A., Taleb A., Bouraghda A., Bouamra A., Demmene Debbih N., Rabia S., Temmar M., Bouafia M.	P1-06: The characteristics of hypertension in postmenopausal women in specialized consultation in the region of Blida (Algeria) [Les caractéristiques de l'HTA chez la femme ménopausée en consultation spécialisée dans la région de Blida (Algérie)]	2015	Annales de Cardiologie et d'Angeiologie	0	10.1016/S0003-3928(16)30053-1	French language
Oummou S., Abardazzou A., El Hattaoui M.	P-223: Management of hypertensive patients with heart failure in Marrakech university hospital [Prise en charge des hypertendus insuffisants cardiaques chroniques au CHU de Marrakech]	2015	Annales de Cardiologie et d'Angeiologie	0	10.1016/S0003-3928(16)30265-7	French language
Derbal S., Ben Kaab B., Jomni M.T., Bellakhel S., Mestiri A., Smida H., Dougui M.H.	P-067: Feature of secondary hypertension [Particularités de l'hypertension artérielle secondaire: à propos de 10 cas]	2015	Annales de Cardiologie et d'Angeiologie	0	10.1016/S0003-3928(16)30111-1	French language
Bachir Cherif A., Taleb A., Bouraghda A., Atif A., Labat C., Chibane A., Temmar M., Benetos A., Bouafia M.	P-127: What specific cardiovascular between black and white hypertensive population in south of Algeria? [Quelles specificités cardiovasculaires entre une population noire hypertendue et blanche hypertendue au sud algérien ?]	2015	Annales de Cardiologie et d'Angeiologie	0	10.1016/S0003-3928(16)30171-8	French language
Bachir Cherif A., Taleb A., Bouraghda A., Bouamra A., Demmene Debbih N., Rabia S., Temmar M., Boua-Fia M.	P-177: Hyperuricemia and cardiovascular risk in hypertensive in specialized consultation in region of Blida (Algeria) [Hyperuricémie et risque cardiovasculaire chez les hypertendus en consultation spécialisée dans la région de Blida (Algérie)]	2015	Annales de Cardiologie et d'Angeiologie	0	10.1016/S0003-3928(16)30220-7	French language

APPENDIX II

- Supplementary Table 1. PubMed search strategy for MENA Health economic research - chapters V and VI.

Health economics	(("outcomes"[Title/Abstract] AND "costs"[Title/Abstract]) OR ("outcomes"[Title/Abstract] AND "cost"[Title/Abstract]) OR ("outcome"[Title/Abstract] AND "costs"[Title/Abstract]) OR ("outcome"[Title/Abstract] AND "cost"[Title/Abstract]) OR ("benefits"[Title/Abstract] AND "costs"[Title/Abstract]) OR ("benefits"[Title/Abstract] AND "cost"[Title/Abstract]) OR ("benefit"[Title/Abstract] AND "costs"[Title/Abstract]) OR ("benefit"[Title/Abstract] AND "cost"[Title/Abstract]) OR "cost saving"[Title/Abstract] OR "cost savings"[Title/Abstract] OR "cost analysis"[Title/Abstract] OR "cost benefit analysis"[Title/Abstract] OR "cost analysis"[Title/Abstract] OR "economic evaluation"[Title/Abstract] OR "economic appraisal"[Title/Abstract] OR "cost effectiveness"[Title/Abstract] OR "cost utility"[Title/Abstract] OR "cost consequence"[Title/Abstract] OR "cost minimization"[Title/Abstract] OR "budget impact"[Title/Abstract] OR "decision model"[Title/Abstract] OR "HTA"[Title/Abstract] OR "health technology assessment"[Title/Abstract] OR "COI"[Title/Abstract] OR "cost of illness"[Title/Abstract] OR "cost of disease"[Title/Abstract] OR "CEA"[Title/Abstract] OR "CBA"[Title/Abstract] OR "CMA"[Title/Abstract] OR "CUA"[Title/Abstract] OR "DALY"[Title/Abstract] OR "QALY"[Title/Abstract] OR "quality adjusted life years"[Title/Abstract] OR "quality adjusted life year"[Title/Abstract] OR "disability-adjusted life years"[Title/Abstract] OR "disability-adjusted life year"[Title/Abstract] OR "ICER"[Title/Abstract] OR "cost effectiveness ratio"[Title/Abstract] OR "ACER"[Title/Abstract] OR "Markov model"[Title/Abstract] OR "quantitative evaluation"[Title/Abstract] OR "decision tree"[Title/Abstract] OR "health economic"[Title/Abstract] OR "discrete event simulation"[Title/Abstract] OR "program evaluation"[Title/Abstract] OR "decision making"[Title/Abstract] OR "expenditure"[Title/Abstract] OR "economic model"[Title/Abstract] OR "friction cost"[Title/Abstract] OR "contingent valuation"[Title/Abstract] OR "medical cost"[Title/Abstract] OR "medical costs"[Title/Abstract] OR "disease related cost"[Title/Abstract] OR "disease related costs"[Title/Abstract] OR "direct cost"[Title/Abstract] OR "direct costs"[Title/Abstract] OR "indirect cost"[Title/Abstract] OR "indirect costs"[Title/Abstract] OR "cost comparison"[Title/Abstract] OR "resource utilization"[Title/Abstract] OR "economic burden"[Title/Abstract] OR "pharmacoeconomic"[Title/Abstract] OR "pharmacy economic"[Title/Abstract] OR "cost effective"[Title/Abstract])
	AND
Countries	egypt11[Title/Abstract] OR egypt24[Title/Abstract] OR egypt35[Title/Abstract] OR egypt7[Title/Abstract] OR egypta5[Title/Abstract] OR egyptae[Title/Abstract] OR egyptain[Title/Abstract] OR egyptalum[Title/Abstract] OR egypte[Title/Abstract] OR egyptensis[Title/Abstract] OR egypti[Title/Abstract] OR egyptia[Title/Abstract] OR egyptiaca[Title/Abstract] OR egyptiacae[Title/Abstract] OR egyptiacum[Title/Abstract] OR egyptiacus[Title/Abstract] OR egyptial[Title/Abstract] OR egyptiam[Title/Abstract] OR egyptian[Title/Abstract] OR egyptian'[Title/Abstract] OR egyptian's[Title/Abstract] OR egyptiandecent[Title/Abstract] OR egyptianellosis[Title/Abstract] OR

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	AND
Filters	(“loattrfull text”[sb] AND English[language])

- Supplementary Table 2. Cost-utility studies from the MENA region

Author, year	Country	Technology	Population	Health Outcome	Costing year	Type of study	Perspective	ICD-10 Chapter	Journ alrank
Almalki, 2019 [46]	KSA[a]	Intensive blood pressure treatment	Pts with hypertension and high cardiovascular risk	QALY[b]	2018	model based	patient	IX Circulatory	Q2
Hersi, 2019 [47]	KSA	Apixaban for stroke prevention	Pts with atrial fibrillation	QALY	2013	model based	health system	XI Digestive	Q3
Al-Senani, 2019 [48]	KSA	Care program development (reperfusion centres)	Pts with stroke	QALY	2018	model based	health system	IX Circulatory	Q1
Knott, 2019 [49]	KSA & other[c]	Erithropoietin	Pts with traumatic brain injury	QALY	2014	trial based	health system	XIX Injury / external	Q1
Cardarelli, 2018 [50]	Iraq; Libya & other	Humanitarian cardiac surgery programs	Paediatric pts with congenital heart disease	DALY[d]	2015	model based	other	XVII Congenital	na
Mostafa, 2019 [51]	Egypt	Safety needles to prevent HBV, HCV and HIV	Pts receiving injections (hypothetical cohort)	QALY	2017	trial based	health system	XIX Injury / external	Q2
Pugh, 2019 [52]	Algeria; Tunisia	Pneumococcus vaccination	Infants	QALY	2016	model based	health system	I Infectious	Q1
Elsisi, 2019 [8]	Egypt	Sorafenib	Pts with hepatocellular carcinoma	QALY	2017	trial based	healthcare institution	II Neoplasms	Q2
Hayajneh, 2018 [53]	Jordan	Hepatitis A vaccination	Infants	QALY	2016	model based	society	I Infectious	Q1
Nuhoho, 2018 [54]	UAE[e]	Paliperidone palmitate	Pts with chronic schizophrenia	QALY	2016	model based	health system	V Mental	Q1
Alsaqa'aby, 2017 [55]	KSA	Oral agents (fingolimod, teriflunomide, dimethyl fumarate) vs interferon	Pts with multiple sclerosis	QALY	2015	model based	health system	VI Nervous	Q3
Al-Aidaroos, 2017 [56]	KSA	Rotavirus vaccination	Infants	QALY	2012	model based	society	I Infectious	Q2
El-Hamamsy, 2016 [57]	Egypt	Warfarin with Low-dose Aspirin vs. Warfarin Alone	Pts with mechanical heart valve prostheses	QALY	2014	trial based	health system	XIX Injury / external	Q1
Faraj, 2016 [58]	Morocco	Insecticide-treated bed nets and indoor residual spraying for prevention	Pts with cutan leishmaniasis in general population	DALY	2013	trial based	healthcare institution	I Infectious	Q1
Estes, 2015 [59]	Egypt	Population treatment scenarios	Pts with Hepatitis C in general population	DALY	2015	model based	society	I Infectious	Q1
Nasef, 2015 [60]	KSA	Celecoxib vs. non-steroidal anti-inflammatory drugsplus proton-pump inhibitors	Pts with osteoarthritis	QALY	2013	model based	patient	XIII Musculo-skeletal	Q2

Sibak, 2015 [61]	Egypt	Pneumococcus vaccination	Infants	DALY	2013	model based	health system	I Infectious	Q1
El Sabaawy, 2015 [62]	Egypt	Pegylated interferon alpha variates	Pts with hepatitis C	QALY	2012	trial based	health system	I Infectious	Q1
Eltabbakh, 2015 [63]	Egypt	Screening program	Pts with hepatocellular carcinoma in general population	QALY	2011	trial based	health system	II Neoplasms	Q3
Alkoshi, 2014 [64]	Libya	Rotavirus vaccination	Infants	QALY	2014	model based	society	I Infectious	Q3
Kim, 2015 [65]	Egypt	Screening and treatment program	Pts with Hepatitis C in general population	QALY	2014	model based	health system	I Infectious	Q1
Aburahma, 2015 [66]	Jordan	Vagus nerve stimulation	Pts with refractory epilepsy	QALY	2011	trial based	health system	VI Nervous	Q2
Gupta, 2015 [67]	KSA & other	Switch to biphasic insulin aspart 30 from other insulin preparations	Pts with type 2 diabetes mellitus	QALY	2013	model based	health system	IV Endocrine	Q1
Home, 2015 [68]	Algeria & other	Insulin detemir	Pts with type 2 diabetes mellitus	QALY	2013	model based	health system	IV Endocrine	Q1
Shafie, 2014 [69]	Algeria, KSA & other	Biphasic insulin aspart 30	Pts with type 2 diabetes mellitus	QALY	2013	model based	health system	IV Endocrine	Q1
Al Awaidy, 2014 [70]	Oman	Rotavirus vaccination	Infants	QALY	2010	model based	society	I Infectious	Q1
Obach, 2014 [71]	Egypt	Immediate vs delayed treatment with pegylater interferon and ribavirin	Pts with hepatitis C	QALY	2012	model based	society	I Infectious	Q1
Kim, 2013 [72]	MENA16f & other	HPV vaccination (cervical cancer prevention)	Pre-adolescent girls	DALY	2010	model based	society	II Neoplasms	Q1
Sutherland, 2013 [73]	Egypt	Non-pneumatic anti-shock garment	Pregnant women with obstetric hemorrhage	DALY	2010	trial based	health system	XV Pregnancy	Q1
Alkire, 2012 [74]	MENA6g & other	Cesarean section	Pregnant women ungergoing caesarean section	DALY	2008	model based	health system	XV Pregnancy	Q1

[a]KSA: Saudi Arabia; [b]QALY: Quality-Adjusted Life-Year; [c]other: countries outside of MENA; [d]DALY: Disability-Adjusted Life-Year; [e]UAE: United Arab Emirates; [f]MENA16: Algeria, Bahrain, Egypt, Iraq, Jordan, KSA, Kuwait, Lebanon, Libya, Morocco, Oman, Qatar, Syria, Tunisia, UAE, Yemen; [g]MENA6: Algeria, Libya, Morocco,Oman, Tunisia, Yemen

- Supplementary Table 3. Full economic evaluations and other methods from the MENA region

Author, year	Country	Technology	Population	Health Outcome	Costing year	Method	Type of study	Perspective	ICD-10 Chapter	Journal rank
Messoudi, 2019 [76]	Morocco	HPV vaccination (cervical cancer prevention)	Pre-adolescent girls	Life year gained	2018	CEA[a]	model based	health system	II Neoplasms	Q2
Kaci, 2019 [77]	Algeria; Egypt	Diagnosis driven vs empirical treatment of invasive fungal infections	Immunocompromised pts with haematological malignancy	Death avoided	2015	CEA	model based	health system	III Blood	Q2
Abushanab, 2019 [78]	Qatar	Morphine vs fentanyl	Paediatric pts (neonates) with respiratory distress syndrome receiving mechanical ventilation	Case of pain relief	2017	CEA	trial based	healthcare institution	XVI Perinatal	Q1
El-Ghitany, 2019 [79]	Egypt	EGCRISK application vs mass screening	Pts with hepatitis C in general population	various	2015	CCA[b]	model based	health system	I Infectious	Q2
Cara, 2018 [80]	KSA[c]	Low vs. high dose colistin	Pts with multidrug-resistant Gram-negative pneumonia	Nephrotoxicity avoided	2013	CEA	trial based	healthcare institution	X Respiratory	Q1
Gamaoun, 2018 [81]	Tunisia	HPV vaccination (cervical cancer prevention)	Pre-adolescent girls	Cervical cancer avoided	2017	CEA	trial based	health system	II Neoplasms	Q1
Alonso, 2017 [82]	Morocco	Diagnostic and therapeutic strategies	Pediatric pts with visceral leishmaniasis	Death avoided	2014	CEA	model based	health system	I Infectious	na
El-Khamery, 2017 [83]	Egypt	Monotherapy options	Pts with glaucoma	Percentage reduction of IOP[d]	2014	CEA	trial based	health system	VII Eye	Q2
Joosub, 2015 [84]	KSA	Imipenem cilastatin vs meropenem	Pts taking carbapenems in hospital	various	2013	CMA[e]	trial based	health system	I Infectious	Q2
Alhelali, 2016 [85]	KSA	Home respiratory therapy services	Pts requiring respiratory therapy	various	2013	CCA	trial based	health system	X Respiratory	Q3
Assanelli, 2015 [86]	Algeria & other[f]	ECG screening	Athletes	Life year gained	2008	CEA	model based	health system	IX Circulatory	Q1
Wilcox, 2015 [87]	Syria	Salt reduction policy for prevention	Pts with coronary heart disease in general population	Life year gained	2010	CEA	model based	other	IX Circulatory	Q1
Mason, 2014 [88]	Palestine; Syria; Tunisia & other	Salt reduction policy for prevention	Pts with coronary heart disease in general population	Life year gained	2010	CEA	model based	society	IX Circulatory	Q1
Connolly, 2012 [89]	Egypt	Rotavirus vaccination	infants	Monetary	2009	CBA[g]	model based	other	I Infectious	Q1

Sladkevicius, 2010 [90]	Libya	Screening program	Paediatric pts with phenylketonuria in neonates	Life year gained	2007	CEA	model based	health system	IV Endocrine	Q2
Nagi, 2005 [91]	Yemen	Infection control programme (chemotherapy and education)	Paediatric pts with schistosomiasis among schoolchildren	Various	2001	CCA	trial based	health system	I Infectious	Q3
Al-Inany, 2006 [92]	Egypt	Human menopausal gonadotrophin vs recombinant follicle stimulating hormone for ovulation induction	Women undergoing in vitro fertilisation	Ongoing pregnancy	2005	CEA	model based	health system	XXI Factors influencing health	Q1
Lahiri, 2005 [93]	MENA14h & other*	Occupational health interventions for prevention	Pts with occupational back pain in general population	Healthy life year gained	2000	CEA	model based	other	XIII Musculoskeletal	Q1
Morris, 2004 [94]	Kuwait	Oral health program	Paediatric dental pts among schoolchildren	various	1998	CCA	trial based	other	XI Digestive	Q2
Vassall, 2002 [95]	Egypt, Syria	Infection control strategies (Directly observed treatment, short course; DOTS)	Pts with tuberculosis	Cured tuberculosis case	1999	CEA	trial based	society	I Infectious	Q1
Talaat, 2000 [96]	Egypt	Infection control programs	Paediatric pts with schistosomiasis in out-of-school population	Infected child treated	1997	CEA	trial based	health system	I Infectious	Q1
Rudgard, 2017 [28]	Yemen & other*	Cash transfer strategies to prevent catastrophic payments	Pts with tuberculosis	Monetary	2013	Other	model based	patient	I Infectious	Q1
Polimeni, 2016 [27]	Jordan	Magnitude of health expenditure (public and out of pocket)	pts with Hepatitis A / diarrhoea in general population	diarrhoea and hepatitis A case	2010	Other	econom etric	health system	I Infectious	Q2
Al-Badriyeh, 2016 [26]	Qatar	Proton pump inhibitors selected with multi-criteria decision analysis	Pts taking proton-pump inhibitors	na	2014	MCDAi	model based	health system	XI Digestive	Q1

aCEA: Cost-Effectiveness Analysis; [b]CCA: Cost-Consequence Analysis; [c]KSA: Saudi Arabia, [d]IOP: Intraocular Pressure; [e]CMA: Cost-Minimisation Analysis; [f]other: countries outside of MENA; [g]CBA: Cost-Benefit Analysis; [h]MENA14: Bahrain; Egypt; Iraq; Jordan; Kuwait; Lebanon; LBY; Morocco; Oman; Qatar; KSA; Syria; Tunisia; Yemen; [i]MCDA: Multiple-Criteria Decision Analysis

- Supplementary Table 4. Partial economic analyses in the MENA region.

Author, year	Country	Technology	Population	Costing year	Type of evaluation	Type of study	Perspective	ICD-10 Chapter	Journal rank
Al-Senani, 2019 [97]	KSA[a]	Acute and rehabilitation service staffing	Pts with stroke	na	BIA[b]	model based	health system	IX Circulatory	Q1
AlBaty, 2019 [98]	KSA	Determinants of catastrophic expenditure (payment methods)	Dental pts	2018	Cost[c]	trial based	patient	XI Digestive	Q2
Elsisi, 2019 [99]	Egypt	Budesonide/formoterol	Pts with asthma	2019	BIA	model based	health system	X Respiratory	Q2
Al-Qudah, 2019 [100]	Jordan	Clinical pharmacist intervention toprevent drug adverse events	Pts with chronic conditions inoutpatient care	2019	BIA	trial based	healthcare institution	XIX Injury / external	Q2
Vallasciani, 2019 [101]	KSA	Telehealth assessment	Paediatric pts with urological conditions	2017	Cost	trial based	patient	XIV Genitourinary	Q1
Morris, 2018 [102]	KSA	Demand management of laboratoryservices	Pts in tertiary hospital	2017	Cost	trial based	healthcare institution	ns	Q3
Assefa, 2017 [103]	Egypt &other[d]	Sofosbuvir differential pricing andlicensing	Pts with hepatitis C	2016	BIA	model based	health system	I Infectious	Q1
Al-Ahmad, 2016 [104]	Kuwait	Omalizumab	Pts with refractory chronicspontaneous urticaria	2014	BIA	model based	health system	IX Circulatory	Q1
Iyengar, 2016 [105]	Egypt &other	Sofosbuvir and ledipasvir/sofosbuvir	Pts with hepatitis C	2014	BIA	model based	health system	I Infectious	Q1
Hamidi, 2016 [106]	UAE[d]	Insurance plans and cost sharingpatterns	Pts using neuropsychiatric services	2014	Cost	trial based	health system	V Mental	Q1
Ahmad, 2016 [107]	Oman	Do not resuscitate policies	Pts undergoing cardiovascularresuscitation	2014	Cost	trial based	health system	ns	Q3
Sabry, 2015 [108]	Egypt	Intravenous to oral paracetamol switch	Pts with postoperative pain	2013	Cost	trial based	health system	XVIII Symptoms	Q2
Younis, 2015 [109]	Palestine	Transplant vs. haemodialysis	Pts with renal failure	na	Cost	model based	health system	XIV Genitourinary	Q1
Aljbouri, 2013 [110]	Jordan	Clinical pharmacist	Pts in intensive care unit	2010	Cost	trial based	healthcare institution	ns	Q2

Al-Sharayri, 2013 [111]	Jordan	Insulin pen vs vial	Pts with diabetes mellitus	2012	Cost	trial based	healthcare institution	IV Endocrine	Q2
Khan, 2013 [112]	Oman	Laparoscopic vs open appendectomy	Paediatric pts undergoing appendectomy	2012	Cost	trial based	health system	XI Digestive	Q3
Bennis, 2012 [113]	Morocco	Fee exemption policy	Pregnant women undergoingcaesarean section	2010	Cost	trial based	patient	XV Pregnancy	Q4
Abuelkhair, 2012 [114]	UAE	Generic prescription policy (proton pump inhibitors, statins, ezetimibe)	Pts taking lipid lowering or proton pump inhibitor drugs	2011	BIA	model based	health system	ns	Q2
Nurgat, 2011 [115]	KSA	Clinical pharmacist intervention through web-based tool	Pts in tertiary hospital	2009	Cost	trial based	healthcare institution	ns	Q1
Alsultan, 2010 [116]	KSA	Inappropriate use of intravenous proton-pump inhibitors	Pts taking intravenous proton pump inhibitors	2008	Cost	trial based	healthcare institution	XI Digestive	Q3
Boutayeb, 2010 [117]	Morocco	Trastuzumab and taxanes	Pts with early breast cancer	2007	BIA	model based	health system	II Neoplasms	Q1
Al-Abbadi, 2009 [118]	Jordan	Joint procurement of pharmaceuticals	Insured pts taking antibiotics, anti- HIV medications or antituberculotic agents	2007	Cost	trial based	health system	ns	Q1
Hamidi, 2008 [119]	Palestine	Essential medicines list	Pts taking medicines in general population	2003	Cost	trial based	health system	ns	Q3
Mawajdeh, 2004 [120]	Jordan	Rationalising primary care staff	Pts in primary care	2001	BIA	model based	health system	ns	Q3
Aasham, 2004 [121]	Oman	Audiometric screening	Paediatric pts with hearing loss among school children	2003	Cost	trial based	health system	VIII Ear	Q3
Fateha, 2001 [122]	Bahrain	Triage	Pts in accident and emergency department	2000	Cost	trial based	healthcare institution	XIX Injury / external	Q2
Yip, 2001 [123]	Egypt	School health insurance program	Schoolchildren	1995	Cost	econo metri c	patient	ns	Q1
Linkins, 1995 [124]	Egypt	House-to-house vs. fixed-site oral poliovirus vaccine delivery	Children	1993	Cost	trial based	health system	ns	na

[a]KSA: Saudi Arabia; [b]BIA: Budget-Impact Analysis; [c]Cost: Cost-comparison; [d]UAE: United Arab Emirate

APPENDIX III

- Supplementary Table 1. Full health economic evaluations by author name, publication year, target country, disease under investigation, corresponding ICD-10 chapter, the intervention as mentioned, data source, number of patients, and the evaluation methodology of the study (Chapter V).

Author, year	Ref.	Target country	Disease (as is)	ICD 10 chapter	Intervention (as is)	Data source	Number of patients	Evaluation type
Hayajneh WA, 2018	BMC Infect Dis. 2018 Mar 7;18(1):119	Jordan (JOR)	hepatitis A infection	I Certain infectious and parasitic diseases	Hepatitis A vaccination	model	8117564	CEA 1
Al-Aidaroos AYA, 2017	J Infect Public Health. 2017 Sep - Oct;10(5):564-571	KSA5 (SAU)	Rotavirus	I Certain infectious and parasitic diseases	Rotavirus vaccination	model	562.428	CEA
Al Quran HA, 2015	J Telemed Telecare. 2015 Mar;21(2):93-9	Jordan (JOR)	skin diseases	XII Diseases of the skin and subcutaneous tissue	real-time teledermatology	Primary study	88	CMA 2
Alkoshi S, 2014	Libyan J Med. 2014 Dec 9;9:26236	Libya (LBY)	children < 5 yo rotavirus infections	I Certain infectious and parasitic diseases	Rotavirus vaccination	primary study	160000	CUA 3
Kim DD, 2015	Glob Public Health. 2015;10(3):296-317	Egypt (EGY)	Pts with Hepatitis C in general population	I Certain infectious and parasitic diseases	Screening and treatment program	secondary study	ns	CEA
Al Awaidy ST, 2014	BMC Infect Dis. 2014 Jun 17;14:334	Oman (OMN)	Rotavirus	I Certain infectious and parasitic diseases	Rotavirus vaccination	secondary study	65500	CUA 3
Connolly MP, 2012	Pharmacoeconomics. 2012 Aug 1;30(8):681-95	Egypt (EGY)	Rotavirus	I Certain infectious and parasitic diseases	Rotavirus vaccination	secondary study	1909000	CBA 4
Vassall A, 2002	Int J Tuberc Lung Dis. 2002 Dec;6(12):1083-90	Egypt (EGY)	tuberculosis	I Certain infectious and parasitic diseases	Infection control strategies (Directly observed treatment, short-course; DOTS)	primary study	150	CEA
Abbas M, 2006	J Egypt Public Health Assoc. 2006;81(1-2):59-73	KSA (SAU)	Influenza	X Diseases of the respiratory system	Workplace influenza vaccination	secondary study	2400	CBA
Salman RA, 2019	BMC Health Serv Res. 2019 Dec	Bahrain (BHR)	Type 2 diabetes	IV Endocrine, nutritional and	type 2 diabetes treatment	primary study	628	COI1

	5;19(1):939			metabolic diseases				
Da'ar OB, 2018	Heliyon. 2018 May 31;4(5):e00637	KSA6 (SAU)	cancer	II Neoplasms	ns	model	10101	COI
Rudgard WE, 2017	PLoS Med. 2017 Nov 7;14(11):e1002418	Yemen (YMD)	tuberculosis	I Certain infectious and parasitic diseases	Cash transfer strategies to prevent catastrophic payments	secondary study	320	COI
Sadat-Ali M, 2015	Arch Osteoporos. 2015;10:37	KSA (SAU)	osteoporosis-related femoral fractures	XIII Diseases of the musculoskeletal system and connective tissue	economic burden of osteoporosis-related femoral fractures	primary study	157764	BoD 2
Al-Kaabi SK, 2015	Clinicoecon Outcomes Res. 2015 Jul 2;7:377-85	Qatar (QAT)	noncommunicable diseases	ns	Impact of noncommunicable diseases in the State of Qatar	secondary study	na	BoD
Alkoshi S, 2015	BMC Public Health. 2015 Jan 24;15:26	Libya (LBY)	Rotavirus	I Certain infectious and parasitic diseases	Rotavirus vaccination	primary study	140	COI
Al-Qadhi W, 2014	BMC Psychiatry. 2014 Jul 3;14:190	KSA (SAU)	Pts with depression in primary care	V Mental and behavioural disorders	Screening program	primary study	477	ErC3
Barakat A, 2013	Pan Afr Med J. 2013;14:42	Egypt (EGY)	diarrhea	I Certain infectious and parasitic diseases	children with diarrhea	primary study	763	BoD
Bennis I, 2012	Arch Public Health. 2012 Jan 3;70(1):3	Morocco (MAR)	Pregnant women undergoing cesarean section	XV Pregnancy, childbirth and the puerperium	Fee exemption policy	primary study	100	CoC4
Othman GQ, 2012	East Mediterr Health J. 2012 Apr;18(4):393-8	Yemen (YMD)	tuberculosis	I Certain infectious and parasitic diseases	costs associated with tuberculosis (TB) diagnosis and treatment for the public health services and patients	primary study	320	COI
Younis MZ, 2011	J Health Care Finance. 2011 Spring;37(3):87-100	Palestine (PSE)	NS	XII Diseases of the skin and subcutaneous tissue	Cardiac Catheterization Services	primary study	1743	CVP 5
Younes M, 2010	Joint Bone Spine. 2010 Jan;77(1):41-6	Tunisia (TUN)	Pts with chronic inflammatory joint disease ankylosing spondylitis	XIII Diseases of the musculoskeletal system and connective tissue	Socioeconomic impact of ankylosing spondylitis	primary study	50	COI
Majorowski MM, 2005	Trans R Soc Trop Med Hyg. 2005 Apr;99(4):268-78	Tunisia (TUN)	Echinococcosis	I Certain infectious and parasitic diseases	a cost analysis of Echinococcosis	model	na	COI
Qari FA, 2001	Saudi Med J. 2001 Oct;22(10):907-9	KSA (SAU)	thyrotoxicosis	IV Endocrine, nutritional and metabolic diseases	Outcome of thyrotoxicosis treatment	primary study	100	ErC

1: CEA: Cost-Effectiveness Analysis; 2: CMA: Cost-Minimisation Analysis 3: Cost-Utility analysis, 4: Cost-Benefit analysis, 5: Kingdom of Saudi Arabia

- Supplementary Table 2. Partial economic evaluations by author name, publication year, target country, disease under investigation, corresponding ICD-10 chapter, the intervention as mentioned, data source, number of patients, and the evaluation methodology of the study.

Author, year	Ref.	Target country	Disease (as is)	ICD 10 chapter	Intervention (as is)	Data source	Number of patients	Evaluation type
Salman RA, 2019	BMC Health Serv Res. 2019 Dec 5;19(1):939	Bahrain (BHR)	Type 2 diabetes	IV Endocrine, nutritional and metabolic diseases	type 2 diabetes treatment	primary study	628	COI1
Da'ar OB, 2018	Heliyon. 2018 May 31;4(5):e00637	KSA6 (SAU)	cancer	II Neoplasms	ns	model	10101	COI
Rudgard WE, 2017	PLoS Med. 2017 Nov 7;14(11):e1002418	Yemen (YMD)	tuberculosis	I Certain infectious and parasitic diseases	Cash transfer strategies to prevent catastrophic payments	secondary study	320	COI
Sadat-Ali M, 2015	Arch Osteoporos. 2015;10:37	KSA (SAU)	osteoporosis-related femoral fractures	XIII Diseases of the musculoskeletal system and connective tissue	economic burden of osteoporosis-related femoral fractures	primary study	157764	BoD2
Al-Kaabi SK, 2015	Clinicoecon Outcomes Res. 2015 Jul 2;7:377-85	Qatar (QAT)	noncommunicable diseases	ns	Impact of noncommunicable diseases in the State of Qatar	secondary study	na	BoD
Alkoshi S, 2015	BMC Public Health. 2015 Jan 24;15:26	Libya (LBY)	Rotavirus	I Certain infectious and parasitic diseases	Rotavirus vaccination	primary study	140	COI
Al-Qadhi W, 2014	BMC Psychiatry. 2014 Jul 3;14:190	KSA (SAU)	Pts with depression in primary care	V Mental and behavioural disorders	Screening program	primary study	477	ErC3
Barakat A, 2013	Pan Afr Med J. 2013;14:42	Egypt (EGY)	diarrhea	I Certain infectious and parasitic diseases	children with diarrhea	primary study	763	BoD
Bennis I, 2012	Arch Public Health. 2012 Jan 3;70(1):3	Morocco (MAR)	Pregnant women undergoing cesarean section	XV Pregnancy, childbirth and the puerperium	Fee exemption policy	primary study	100	CoC4
Othman GQ, 2012	East Mediterr Health J. 2012 Apr;18(4):393-8	Yemen (YMD)	tuberculosis	I Certain infectious and parasitic diseases	costs associated with tuberculosis (TB) diagnosis and treatment for the public health services and patients	primary study	320	COI
Younis MZ,	J Health Care Finance.	Palestine	NS	XII Diseases of the	Cardiac Catheterization Services	primary	1743	CVP5

2011	2011 Spring;37(3):87-100	(PSE)		skin and subcutaneous tissue		study		
Younes M, 2010	Joint Bone Spine. 2010 Jan;77(1):41-6	Tunisia (TUN)	Pts with chronic inflammatory joint disease ankylosing spondylitis	XIII Diseases of the musculoskeletal system and connective tissue	Socioeconomic impact of ankylosing spondylitis	primary study	50	COI
Majorowski MM, 2005	Trans R Soc Trop Med Hyg. 2005 Apr;99(4):268-78	Tunisia (TUN)	Echinococcosis	I Certain infectious and parasitic diseases	a cost analysis of Echinococcosis	model	na	COI
Qari FA, 2001	Saudi Med J. 2001 Oct;22(10):907-9	KSA (SAU)	thyrotoxicosis	IV Endocrine, nutritional and metabolic diseases	Outcome of thyrotoxicosis treatment	primary study	100	ErC

1: Cost of illness study, 2: Burden of disease, 3: Efficacy study reporting costs, 4: Cost comparison, 5: Cost volume profit analysis 6: Kingdom of Saudi Arabia

- Supplementary Table 3. Extracted PL cost items (n=95).

PL item no.	Cost city	ICD 10 name	ICD 10 code	ICD 10 chapter	Cost description (as is)	Cost	Patient population	Currency	PL item Type
1	Bahrain (BHR)	Type 2 diabetes mellitus	E11.8	IV Endocrine, nutritional and metabolic diseases	total indirect costs due to absenteeism	1,230,000.00	na	BHD	absenteeism
2	KSA (SAU)	Malignant (primary) neoplasm, unspecified	C80.1	II Neoplasms	the net present value of non-health GDP lost due to cancer deaths among Saudi female population aged 15e60 years	1,460,339,286.00	non-health GDP loss per female patient	USD	mortality PL
3	KSA (SAU)	Malignant (primary) neoplasm, unspecified	C80.1	II Neoplasms	the net present value of nonhealth GDP lost due to cancer deaths among Saudi male population aged 15e60 years	1,107,004,886.00	non-health GDP loss per male patient	USD	mortality PL
4	Jordan (JOR)	Acute hepatities A	B15	I Certain infectious and parasitic diseases	Total Cost Savings(Including indirect costs): 10y	3,690,000.00	per vaccinated person (Indirect costs included the costs associated with the work loss due to different health outcomes)	USD	total cost (incl. PL)
5	Jordan (JOR)	Acute hepatities A	B15	I Certain infectious and parasitic diseases	Total Cost Savings(Including indirect costs):25y	20,030,000.00	per vaccinated person (Indirect costs included the costs associated with the work loss due to different health outcomes)	USD	total cost (incl. PL)
6	Jordan (JOR)	Acute hepatities A	B15	I Certain infectious and parasitic diseases	Total Cost Savings(Including indirect costs): 50y	42,600,000.00	per vaccinated person (Indirect costs included the costs associated with the work loss due to different health outcomes)	USD	total cost (incl. PL)
7	Yemen (YMD)	Tuberculosis	A15-A19	I Certain infectious and parasitic diseases	Reported TB-related costs : indirect	253.00	per patient per year with active DS TB disease	PPP$	absenteeism
8	Yemen (YMD)	Tuberculosis	A15-A19	I Certain infectious and parasitic diseases	Reported TB-related costs :Total	885.00	per patient per year with active DS TB disease	PPP$	total cost (incl. PL)
9	KSA (SAU)	Rotaviral enteritis	A08.0	I Certain infectious and parasitic diseases	Labor cost per day per woman	200.00	per day per woman	SAR	absenteeism
10	KSA (SAU)	Osteoporosis with pathological fracture	M80	XIII Diseases of the musculoskeletal system and connective tissue	Total	2,359,000,000.00	Annual cost	SAR	total cost (incl. PL)
11	KSA (SAU)	Osteoporosis with pathological fracture	M80	XIII Diseases of the musculoskeletal system and connective tissue	Indirect costs calculated as per Bleibler et al. (It was reported that the indirect costs for the first years three times the direct costs-opprtunity cost)	1,690,000,000.00	Annual cost	SAR	absenteeism
12	Qatar (QAT)	ns	ns	ns	total direct and indirect costs for the NCDs (cardiovascular diseases, mental health and behavioral disorders, cancer, respiratory diseases, and diabetes) in the Gulf Cooperation Council region	36,200,000,000.00	for year 2013	USD	total cost (incl. PL)

13	Qatar (QAT)	ns	ns	ns	total indirect costs for the NCDs (cardiovascular diseases, mental health and behavioral disorders, cancer, respiratory diseases, and diabetes) in the Gulf Cooperation Council region	31,000,000,000.00	for year 2013	USD	absenteeism
14	Libya (LBY)	Rotaviral enteritis	A08.0	I Certain infectious and parasitic diseases	Total cost	678.99	per patient	USD	total cost (incl. PL)
15	Libya (LBY)	Rotaviral enteritis	A08.0	I Certain infectious and parasitic diseases	Total from patient perspective	190.88	per patient	USD	absenteeism
16	Libya (LBY)	Rotaviral enteritis	A08.0	I Certain infectious and parasitic diseases	Patient perspective: Lost income by caregiver	42.37	per patient	USD	caregiver PL
17	Jordan (JOR)	Disorder of the skin and subcutaneous tissue, unspecified	L98.9	XII Diseases of the skin and subcutaneous tissue	patients perceived that the cost would be 73.0 JD per visit if they needed to visit the specialist clinic and receive care at the main hospital in Amman.	73.00	clinical care visit (including transportation)	JOD	total cost (incl. PL)
18	Libya (LBY)	Rotaviral enteritis	A08.0	I Certain infectious and parasitic diseases	Cost indirect loss mild/event	36.00	per patient per event	USD	absenteeism
19	Libya (LBY)	Rotaviral enteritis	A08.0	I Certain infectious and parasitic diseases	Cost indirect loss moderate/event	12.00	per patient per event	USD	absenteeism
20	Libya (LBY)	Rotaviral enteritis	A08.0	I Certain infectious and parasitic diseases	Cost indirect loss severe/event	36.00	per patient per event	USD	absenteeism
21	Libya (LBY)	Rotaviral enteritis	A08.0	I Certain infectious and parasitic diseases	Total Productivity loss cost in case of no vaccination	2,711.68	total patient population PL due to sick leave	USD	absenteeism
22	Libya (LBY)	Rotaviral enteritis	A08.0	I Certain infectious and parasitic diseases	Total Productivity loss cost in case of vaccination	1,669.97	total patient population PL due to sick leave	USD	absenteeism
23	Libya (LBY)	Rotaviral enteritis	A08.0	I Certain infectious and parasitic diseases	Total indirect cost/child in case of no vaccination	74.09	per patient	USD	absenteeism
24	Libya (LBY)	Rotaviral enteritis	A08.0	I Certain infectious and parasitic diseases	Total cost/child in case of vaccination	57.83	per patient	USD	total cost (incl. PL)
25	Libya (LBY)	Rotaviral enteritis	A08.0	I Certain infectious and parasitic diseases	The total contribution of patient cost	186.00	One patient contribution	USD	absenteeism
26	Libya (LBY)	Rotaviral enteritis	A08.0	I Certain infectious and parasitic diseases	Total cost in case of no vaccination	11,854,468.00	Including the indirect cost (US$) in the economic evaluation of the vaccine	USD	total cost (incl. PL)
27	Libya (LBY)	Rotaviral enteritis	A08.0	I Certain infectious and parasitic diseases	Total cost in case of no vaccination	9,235,732.00	Including the indirect cost (US$) in the economic evaluation of the vaccine	USD	total cost (incl. PL)
28	Libya (LBY)	Rotaviral enteritis	A08.0	I Certain infectious and parasitic	The cost of the loss of production	40.68	Per patient, lost income due to rotavirus treatment among children aged<5 per	USD	absenteeism

				diseases			patient		
29	Egypt (EGY)	Chronic viral hepatitis C	B18.2	I Certain infectious and parasitic diseases	Productivity loss	44.00	per patient per treatment cycle	USD	absenteeism
30	KSA (SAU)	Depression	F32	V Mental and behavioural disorders	Suicide	350,000.00	per life lost	SAR	mortality PL
31	KSA (SAU)	Depression	F32	V Mental and behavioural disorders	Absenteeism	8,000.00	per patient per month	SAR	absenteeism
32	KSA (SAU)	Depression	F32	V Mental and behavioural disorders	Presenteeism	8,000.00	per patient per month	SAR	presenteisim PL
33	KSA (SAU)	Depression	F32	V Mental and behavioural disorders	Total indirect costs	1,300,000.00	for 1000 persons screened for depression in primary healthcare setting per year	SAR	absenteeism
34	KSA (SAU)	Depression	F32	V Mental and behavioural disorders	Grand total costs (direct+indirect)	1,619,000.00	for 1000 persons screened for depression in primary healthcare setting per year	SAR	total cost (incl. PL)
35	KSA (SAU)	Depression	F32	V Mental and behavioural disorders	Caregiver time lost value	4,000.00	per patient per month	SAR	caregiver PL
36	Oman (OMN)	Rotaviral enteritis	A08.0	I Certain infectious and parasitic diseases	The cost of a day of missed work	29.64	One day of missed work per patient	USD	absenteeism
37	Oman (OMN)	Rotaviral enteritis	A08.0	I Certain infectious and parasitic diseases	The cost of work days lost with no vaccination program	874,985.80	Total population work days lost with no vaccination program	USD	absenteeism
38	Oman (OMN)	Rotaviral enteritis	A08.0	I Certain infectious and parasitic diseases	societal costs with no vaccination program	5,259,899.00	Annual cost	USD	absenteeism
39	Oman (OMN)	Rotaviral enteritis	A08.0	I Certain infectious and parasitic diseases	societal costs with vaccination program	1,153,409.00	Annual cost	USD	absenteeism
40	Oman (OMN)	Rotaviral enteritis	A08.0	I Certain infectious and parasitic diseases	The cost of work days lost with universal vaccination program	233,370.80	Total population work days lost with universal vaccination program	USD	absenteeism
41	Oman (OMN)	Rotaviral enteritis	A08.0	I Certain infectious and parasitic diseases	Indirect (work days lost) costs with no vaccination program	874,985.80	Annual cost	USD	absenteeism
42	Oman (OMN)	Rotaviral enteritis	A08.0	I Certain infectious and parasitic diseases	Indirect (work days lost) costs with universal vaccination program	233,370.80	Annual cost	USD	absenteeism
43	Egypt (EGY)	Diarrhoea	A09.0	I Certain infectious and parasitic diseases	Cost due to absence from work	3.30	per patient per visit	USD	absenteeism
44	Egypt (EGY)	Diarrhoea	A09.0	I Certain infectious and parasitic diseases	total indirect	1.66	per patient per visit	USD	absenteeism

45	Morocco (MAR)	Single delivery by cesarean section	O82	XV Pregnancy, childbirth and the puerperium	Opportunity cost (SEGMA hospital)	8.00	per patient	USD	caregiver PL
46	Morocco (MAR)	Single delivery by cesarean section	O82	XV Pregnancy, childbirth and the puerperium	Opportunity cost (University hospital)	7.00	per patient	USD	caregiver PL
47	Egypt (EGY)	Rotaviral enteritis	A08.0	I Certain infectious and parasitic diseases	Cost resulting from a RV death case	757,295.00	Yearly tax lost due to RV deaths, $US	USD	mortality PL
48	Yemen (YMD)	Respiratory tuberculosis, bacteriologically and histologically confirmed	A15	I Certain infectious and parasitic diseases	Costs borne by patients for pulmonary tuberculosis (TB) treatment	108.40	per patient	USD	total cost (incl. PL)
49	Yemen (YMD)	Respiratory tuberculosis, bacteriologically and histologically confirmed	A15	I Certain infectious and parasitic diseases	Costs borne by patients for extrapulmonary TB treatment	328.00	per patient	USD	total cost (incl. PL)
50	Yemen (YMD)	Respiratory tuberculosis, bacteriologically and histologically confirmed	A15	I Certain infectious and parasitic diseases	Cost to patients for pulmonary tuberculosis (TB) treatment_Time away from work	73.10	per patient	USD	absenteeism
51	Yemen (YMD)	Respiratory tuberculosis, bacteriologically and histologically confirmed	A15	I Certain infectious and parasitic diseases	Cost to patients for extrapulmonary TB treatment-Time away from work	51.90	per patient	USD	absenteeism
52	Yemen (YMD)	Respiratory tuberculosis, bacteriologically and histologically confirmed	A15	I Certain infectious and parasitic diseases	total Cost per patient for pulmonary tuberculosis (TB) treatment for 8 months	17,336.00	per patient for 8 months	USD	total cost (incl. PL)
53	Yemen (YMD)	Respiratory tuberculosis, bacteriologically and histologically confirmed	A15	I Certain infectious and parasitic diseases	Cost to patients for pulmonary tuberculosis (TB) treatment for 8 months : Cost per patient (Time away from work)	73.10	per patient	USD	absenteeism
54	Yemen (YMD)	Respiratory tuberculosis, bacteriologically and histologically confirmed	A15	I Certain infectious and parasitic diseases	total Cost per patient for extrapulmonary TB treatment for 12 months	52,472.00	per patient for 12 months	USD	total cost (incl. PL)

55	Yemen (YMD)	Respiratory tuberculosis, bacteriologically and histologically confirmed	A15	I Certain infectious and parasitic diseases	Cost to patients for extrapulmonary TB treatment for 12 months : Cost per patient (Time away from work)	51.90	per patient	USD	absenteeism
56	Palestine (PSE)	na	Y84.0	XII Diseases of the skin and subcutaneous tissue	patient time loss	16.60	time costs	USD	absenteeism
57	Tunisia (TUN)	Ankylosing spondylitis	M45	XIII Diseases of the musculoskeletal system and connective tissue	Sick leave	263.17	Indirect costs due to sick leave per patient per year	EUR	absenteeism
58	Tunisia (TUN)	Ankylosing spondylitis	M45	XIII Diseases of the musculoskeletal system and connective tissue	Direct + indirect costs	1,060.49	per patient per year	TND	total cost (incl. PL)
59	Tunisia (TUN)	Ankylosing spondylitis	M45	XIII Diseases of the musculoskeletal system and connective tissue	Sick leave, per day (mean)	21.46	per patient per day	TND	absenteeism
60	Tunisia (TUN)	Ankylosing spondylitis	M45	XIII Diseases of the musculoskeletal system and connective tissue	mean annual indirect cost	1,864.80	per patient on sick leave	TND	absenteeism
61	Tunisia (TUN)	Ankylosing spondylitis	M45	XIII Diseases of the musculoskeletal system and connective tissue	mean annual indirect cost	658.20	per working patient	TND	absenteeism
62	Tunisia (TUN)	Echinococcosis, unspecified, of liver	B67.8	I Certain infectious and parasitic diseases	average total cost (including PL)	6,321,000.00	per year	USD	total cost (incl. PL)
63	Tunisia (TUN)	Echinococcosis, unspecified, of liver	B67.8	I Certain infectious and parasitic diseases	Average total cost using defined distributions (including PL)	4,601,000.00	per year	USD	total cost (incl. PL)
64	Tunisia (TUN)	Echinococcosis, unspecified, of liver	B67.8	I Certain infectious and parasitic diseases	PL amounted to nearly 70% of total costs	4,424,700.00	per year	USD	absenteeism
65	Tunisia (TUN)	Echinococcosis, unspecified, of liver	B67.8	I Certain infectious and parasitic diseases	PL amounted to nearly 70% of total costs (defined distribution)	3,220,700.00	per year	USD	absenteeism
66	Syria (SYR)	Tuberculosis	A15-A19	I Certain infectious and parasitic diseases	DOTS/PHC : Patient Time costs (US$) per case treated with directly observed treatment, short-course at primary health care in Syria	18.00	Patient costs (US$) per case treated	USD	total cost (incl. PL)
67	Syria (SYR)	Tuberculosis	A15-A19	I Certain infectious and parasitic diseases	Non-DOTS/SC: Patient Time costs (US$) per case treated with non - directly observed treatment, short-course at specialized clinics in Syria	19.00	Patient costs (US$) per case treated	USD	total cost (incl. PL)
68	Egypt (EGY)	Tuberculosis	A15-A19	I Certain infectious and parasitic	DOTS/PHC: Patient Time costs (US$) per case treated with directly observed	3.00	Patient costs (US$) per case treated	USD	total cost (incl. PL)

				diseases	treatment, short-course at primary health care in egypt				
69	Egypt (EGY)	Tuberculosis	A15-A19	I Certain infectious and parasitic diseases	DOTS/SC: Patient Time costs (US$) per case treated with directly observed treatment, short-course at specialized clinics in Egypt	5.00	Patient costs (US$) per case treated	USD	total cost (incl. PL)
70	Egypt (EGY)	Tuberculosis	A15-A19	I Certain infectious and parasitic diseases	DOTS/hospital/SC: Patient Time costs (US$) per case treated with directly observed treatment, short-course at primary health clinics with hospitilzation in Egypt	240.00	Patient costs (US$) per case treated	USD	total cost (incl. PL)
71	Egypt (EGY)	Tuberculosis	A15-A19	I Certain infectious and parasitic diseases	DOTS/hospital/SC: Patient Time costs (US$) per case treated with directly observed treatment, short-course at primary healthcare with hospitalization in Egypt	229.00	Patient costs (US$) per case treated	USD	total cost (incl. PL)
72	Egypt (EGY)	Tuberculosis	A15-A19	I Certain infectious and parasitic diseases	Non-DOTS/SC: Patient Time costs (US$) per case treated with non - directly observed treatment, short-course at specialized clinics in Egypt	2.00	Patient costs (US$) per case treated	USD	total cost (incl. PL)
73	Egypt (EGY)	Tuberculosis	A15-A19	I Certain infectious and parasitic diseases	Non-DOTS/hospital/SC: Patient Time costs (US$) per case treated with Non-directly observed treatment, short-course at specialized clinics with hospitilzation in Egypt	232.00	Patient costs (US$) per case treated	USD	total cost (incl. PL)
74	KSA (SAU)	Influenza and pneumonia	J09-J18	X Diseases of the respiratory system	Cost of Total time spent on vaccination for vaccination group among the Chemical Industry Workers	8,500.00	per 834 workers	SAR	presenteisim PL
75	KSA (SAU)	Influenza and pneumonia	J09-J18	X Diseases of the respiratory system	Total costs of vaccination among the Chemical Industry Workers	25,180.00	per 834 workers	SAR	total cost (incl. PL)
76	KSA (SAU)	Influenza and pneumonia	J09-J18	X Diseases of the respiratory system	Costs of sick-leave days for no vaccine group among the Chemical Industry Workers	125,000.00	Per 4 months follow up period	SAR	absenteeism
77	KSA (SAU)	Influenza and pneumonia	J09-J18	X Diseases of the respiratory system	Costs of sick-leave days for vaccination group among the Chemical Industry Workers	50,000.00	Per 4 months follow up period	SAR	absenteeism
78	KSA (SAU)	Influenza and pneumonia	J09-J18	X Diseases of the respiratory system	Indirect costs of ILI for no vaccine group among the Chemical Industry Workers	125,000.00	Per 4 months follow up period	SAR	absenteeism
79	KSA (SAU)	Influenza and pneumonia	J09-J18	X Diseases of the respiratory system	Indirect costs of ILI for vaccination group among the Chemical Industry Workers	50,000.00	Per 4 months follow up period	SAR	absenteeism
80	KSA (SAU)	Influenza and pneumonia	J09-J18	X Diseases of the respiratory system	Total costs for no vaccine group among the Chemical Industry Workers	253,160.00	Per 338 workers	SAR	total cost (incl. PL)
81	KSA (SAU)	Influenza and pneumonia	J09-J18	X Diseases of the respiratory system	Total costs for vaccination group among the Chemical Industry Workers	101,200.00	Per 562 worker	SAR	total cost (incl. PL)
82	KSA (SAU)	Influenza and pneumonia	J09-J18	X Diseases of the respiratory system	Cost of Total time spent on vaccination for vaccination group among the Food Processing Industry Workers	1,350.00	per 562 workers	SAR	presenteisim PL
83	KSA (SAU)	Influenza and pneumonia	J09-J18	X Diseases of the respiratory system	Total costs of vaccination among the Food Processing Industry Workers	12,590.00	per 562 workers	SAR	total cost (incl. PL)
84	KSA (SAU)	Influenza and pneumonia	J09-J18	X Diseases of the respiratory system	Costs of sick-leave days for no vaccine group among the Food Processing	86,800.00	Per 4 months follow up period	SAR	absenteeism

					Industry Workers				
85	KSA (SAU)	Influenza and pneumonia	J09-J18	X Diseases of the respiratory system	Costs of sick-leave days for vaccination group among the Food Processing Industry Workers	22,000.00	Per 4 months follow up period	SAR	absenteeism
86	KSA (SAU)	Influenza and pneumonia	J09-J18	X Diseases of the respiratory system	Indirect costs of ILI for no vaccine group among the Food Processing Industry Workers	86,800.00	Per 4 months follow up period	SAR	absenteeism
87	KSA (SAU)	Influenza and pneumonia	J09-J18	X Diseases of the respiratory system	Indirect costs of ILI for vaccination group among the Food Processing Industry Workers	22,000.00	Per 4 months follow up period	SAR	absenteeism
88	KSA (SAU)	Influenza and pneumonia	J09-J18	X Diseases of the respiratory system	Total costs for no vaccine group among the Food Processing Industry Workers	166,300.00	per 338 workers	SAR	total cost (incl. PL)
89	KSA (SAU)	Influenza and pneumonia	J09-J18	X Diseases of the respiratory system	Total costs for vaccination group among the Food Processing Industry Workers	58,400.00	per 562 workers	SAR	total cost (incl. PL)
90	KSA (SAU)	Influenza and pneumonia	J09-J18	X Diseases of the respiratory system	Total costs of vaccination for vaccination groups among the two groups of workers	37,770.00	per 1396 workers	SAR	total cost (incl. PL)
91	KSA (SAU)	Influenza and pneumonia	J09-J18	X Diseases of the respiratory system	Indirect costs of ILI for no vaccine group among the two groups of workers	211,800.00	Per 4 months follow up period	SAR	absenteeism
92	KSA (SAU)	Influenza and pneumonia	J09-J18	X Diseases of the respiratory system	Indirect costs of ILI for vaccination group among the two groups of workers	72,000.00	Per 4 months follow up period	SAR	absenteeism
93	KSA (SAU)	Influenza and pneumonia	J09-J18	X Diseases of the respiratory system	Total costs for no vaccine group among the two groups of workers	419,460.00	per 1004 workers	SAR	total cost (incl. PL)
94	KSA (SAU)	Influenza and pneumonia	J09-J18	X Diseases of the respiratory system	Total costs for vaccination group among the two groups of workers	147,010.00	per 1396 workers	SAR	total cost (incl. PL)
95	KSA (SAU)	Thyrotoxicosis [hyperthyroidism]	E05.90	IV Endocrine, nutritional and metabolic diseases	the cost of surgery + admission,investigations, follow up and time loss	40,000.00	per patient	SAR	total cost (incl. PL)

- Supplementary Table 4. Identification map for PL reporting studies in the MENA region.

ICD 10 chapter	ICD 10 name	Intervention (as is)	Cost country	Analysis type	Currency	Reference
I Certain infectious and parasitic diseases	Acute hepatities A	Hepatitis A vaccination	Jordan (JOR)	CEA	USD	BMC Infect Dis. 2018 Mar 7;18(1):119
	Chronic viral hepatitis C	Screening and treatment program	Egypt (EGY)	CEA	USD	Glob Public Health. 2015;10(3):296-317
	Diarrhoea	children with diarrhea	Egypt (EGY)	BoD	USD	Pan Afr Med J. 2013;14:42
	Echinococcosis, unspecified, of liver	a cost analysis of Echinococcosis	Tunisia (TUN)	COI	USD	Trans R Soc Trop Med Hyg. 2005 Apr;99(4):268-78
	Respiratory tuberculosis, bacteriologically and histologically confirmed	costs associated with tuberculosis (TB) diagnosis and treatment for the public health services and patients	Yemen (YMD)	COI	USD	East Mediterr Health J. 2012 Apr;18(4):393-8
	Rotaviral enteritis	Rotavirus vaccination	Egypt (EGY)	CBA	USD	Pharmacoeconomics. 2012 Aug 1;30(8):681-95
			KSA (SAU)	CEA	SAR	J Infect Public Health. 2017 Sep - Oct;10(5):564-571
			Libya (LBY)	COI	USD	BMC Public Health. 2015 Jan 24;15:26
				CUA	USD	Libyan J Med. 2014 Dec 9;9:26236
			Oman (OMN)	CUA	USD	BMC Infect Dis. 2014 Jun 17;14:334
	Tuberculosis	Cash transfer strategies to prevent catastrophic payments	Yemen (YMD)	COI	PPP$	PLoS Med. 2017 Nov 7;14(11):e1002418
		Infection control strateges (Directly observed treatment, short-course; DOTS)	Egypt (EGY)	CEA	USD	Int J Tuberc Lung Dis. 2002 Dec;6(12):1083-90
II Neoplasms	Malignant (primary) neoplasm, unspecified	NS	KSA (SAU)	COI	USD	Heliyon. 2018 May 31;4(5):e00637
IV Endocrine, nutritional and metabolic diseases	Thyrotoxicosis [hyperthyroidism]	Outcome of thyrotoxicosis treatment	KSA (SAU)	ErC	SAR	Saudi Med J. 2001 Oct;22(10):907-9
	Type 2 diabetes mellitus	type 2 diabetes treatment	Bahrain (BHR)	COI	BHD	BMC Health Serv Res. 2019 Dec 5;19(1):939
ns	ns	Impact of noncommunicable diseases in the State of Qatar	Qatar (QAT)	BoD	USD	Clinicoecon Outcomes Res. 2015 Jul 2;7:377-85

V Mental and behavioural disorders	Depression	Screening program	KSA (SAU)	ErC	SAR	BMC Psychiatry. 2014 Jul 3;14:190
X Diseases of the respiratory system	Influenza and pneumonia	WORKPLACE INFLUENZA VACCINATION	KSA (SAU)	CBA	SAR	J Egypt Public Health Assoc. 2006;81(1-2):59-73
XII Diseases of the skin and subcutaneous tissue	Disorder of the skin and subcutaneous tissue, unspecified	real-time teledermatology	Jordan (JOR)	CMA	JOD	J Telemed Telecare. 2015 Mar;21(2):93-9
	na	Cardiac Catheterization Services	Palestine (PSE)	CVP	USD	J Health Care Finance. 2011 Spring;37(3):87-100
XIII Diseases of the musculoskeletal system and connective tissue	Ankylosing spondylitis	Socioeconomic impact of ankylosing spondylitis	Tunisia (TUN)	COI	TND	Joint Bone Spine. 2010 Jan;77(1):41-6
	Osteoporosis with pathological fracture	economic burden of osteoporosis-related femoral fractures	KSA (SAU)	BoD	SAR	Arch Osteoporos. 2015;10:37
XV Pregnancy, childbirth and the puerperium	Single delivery by cesarean section	Fee exemption policy	Morocco (MAR)	CoC	USD	Arch Public Health. 2012 Jan 3;70(1):3

- Supplementary tables 5. Statistical associations results for MENA PL cost Items

ICD 10 chapter * income grp

Crosstab

			income grp		
			High income	Middle income	Total
ICD 10 chapter	I Certain infectious and parasitic diseases	Count	8	43	51
		% within ICD 10 chapter	15.7%	84.3%	100.0%
	II Neoplasms	Count	2	0	2
		% within ICD 10 chapter	100.0%	0.0%	100.0%
	IV Endocrine, nutritional and metabolic diseases	Count	2	0	2
		% within ICD 10 chapter	100.0%	0.0%	100.0%
	ns	Count	2	0	2
		% within ICD 10 chapter	100.0%	0.0%	100.0%
	V Mental and behavioural disorders	Count	6	0	6
		% within ICD 10 chapter	100.0%	0.0%	100.0%
	X Diseases of the respiratory system	Count	21	0	21
		% within ICD 10 chapter	100.0%	0.0%	100.0%
	XII Diseases of the skin and subcutaneous tissue	Count	0	2	2
		% within ICD 10 chapter	0.0%	100.0%	100.0%
		Count	2	5	7

	XIII Diseases of the musculoskeletal system and connective tissue	% within ICD 10 chapter	28.6%	71.4%	100.0%
	XV Pregnancy, childbirth and the puerperium	Count	0	2	2
		% within ICD 10 chapter	0.0%	100.0%	100.0%
Total		Count	43	52	95
		% within ICD 10 chapter	45.3%	54.7%	100.0%

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	62.009[a]	8	.000
Likelihood Ratio	78.156	8	**.000**
Linear-by-Linear Association	18.317	1	.000
N of Valid Cases	95		

a. 14 cells (77.8%) have expected count less than 5. The minimum expected count is .91.

Symmetric Measures

		Value	Approximate Significance
Nominal by Nominal	Phi	.808	.000
	Cramer's V	**.808**	.000
N of Valid Cases		95	

Type of study * income grp

Crosstab

			income grp		
			High income	Middle income	Total
Type of study	model	Count	3	13	16
		% within Type of study	18.8%	81.3%	100.0%
	primary study	Count	10	35	45
		% within Type of study	22.2%	77.8%	100.0%
	secondary study	Count	30	4	34
		% within Type of study	88.2%	11.8%	100.0%
Total		Count	43	52	95
		% within Type of study	45.3%	54.7%	100.0%

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	39.523[a]	2	**.000**
Likelihood Ratio	43.098	2	.000
Linear-by-Linear Association	30.467	1	.000

N of Valid Cases	95		

a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 7.24.

Symmetric Measures

		Value	Approximate Significance
Nominal by Nominal	Phi	.645	.000
	Cramer's V	**.645**	.000
N of Valid Cases		95	

Full/partial * income grp

Crosstab

			income grp		
			High income	Middle income	Total
Full/partial	Full	Count	29	25	54
		% within Full/partial	53.7%	46.3%	100.0%
	Partial	Count	14	27	41
		% within Full/partial	34.1%	65.9%	100.0%
Total		Count	43	52	95
		% within Full/partial	45.3%	54.7%	100.0%

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	3.598[a]	1	.058		
Continuity Correction[b]	2.852	1	.091		
Likelihood Ratio	3.637	1	.057		
Fisher's Exact Test				**.065**	**.045**
Linear-by-Linear Association	3.560	1	.059		
N of Valid Cases	95				

a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 18.56.
b. Computed only for a 2x2 table

Symmetric Measures

		Value	Approximate Significance
Nominal by Nominal	Phi	.195	.058
	Cramer's V	**.195**	.058
N of Valid Cases		95	

PL item Type * income grp

Crosstab

			income grp		
			High income	Middle income	Total
PL item Type	absenteeism	Count	23	24	47
		% within PL item Type	48.9%	51.1%	100.0%
	caregiver PL	Count	1	3	4

		% within PL item Type	25.0%	75.0%	100.0%
	mortality PL	Count	3	1	4
		% within PL item Type	75.0%	25.0%	100.0%
	presenteisim PL	Count	3	0	3
		% within PL item Type	100.0%	0.0%	100.0%
	total cost including PL	Count	13	24	37
		% within PL item Type	35.1%	64.9%	100.0%
Total		Count	43	52	95
		% within PL item Type	45.3%	54.7%	100.0%

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	7.506[a]	4	.111
Likelihood Ratio	8.739	4	**.068**
Linear-by-Linear Association	.852	1	.356
N of Valid Cases	95		

a. 6 cells (60.0%) have expected count less than 5. The minimum expected count is 1.36.

Symmetric Measures

		Value	Approximate Significance
Nominal by Nominal	Phi	.281	.111
	Cramer's V	.281	.111
N of Valid Cases		95	

Crosstabs - ICD 10 chapter * PL item Type

Case Processing Summary

	Cases					
	Valid		Missing		Total	
	N	Percent	N	Percent	N	Percent
ICD 10 chapter * PL item Type	95	100.0%	0	0.0%	95	100.0%

ICD 10 chapter * PL item Type Crosstabulation

			PL item Type					Total
			absenteeism	caregiver PL	mortality PL	presenteisim PL	total cost including PL	
ICD 10 chapter	I Certain infectious and parasitic diseases	Count	27	1	1	0	22	51
		% within ICD 10 chapter	52.9%	2.0%	2.0%	0.0%	43.1%	100.0%
	II Neoplasms	Count	0	0	2	0	0	2
		% within ICD 10 chapter	0.0%	0.0%	100.0%	0.0%	0.0%	100.0%
	IV Endocrine, nutritional and metabolic diseases	Count	1	0	0	0	1	2

		% within ICD 10 chapter	50.0%	0.0%	0.0%	0.0%	50.0%	100.0%
	ns	Count	1	0	0	0	1	2
		% within ICD 10 chapter	50.0%	0.0%	0.0%	0.0%	50.0%	100.0%
	V Mental and behavioural disorders	Count	2	1	1	1	1	6
		% within ICD 10 chapter	33.3%	16.7%	16.7%	16.7%	16.7%	100.0%
	X Diseases of the respiratory system	Count	10	0	0	2	9	21
		% within ICD 10 chapter	47.6%	0.0%	0.0%	9.5%	42.9%	100.0%
	XII Diseases of the skin and subcutaneous tissue	Count	1	0	0	0	1	2
		% within ICD 10 chapter	50.0%	0.0%	0.0%	0.0%	50.0%	100.0%
	XIII Diseases of the musculoskeletal system and connective tissue	Count	5	0	0	0	2	7
		% within ICD 10 chapter	71.4%	0.0%	0.0%	0.0%	28.6%	100.0%
	XV Pregnancy, childbirth and the puerperium	Count	0	2	0	0	0	2
		% within ICD 10 chapter	0.0%	100.0%	0.0%	0.0%	0.0%	100.0%
Total		Count	47	4	4	3	37	95
		% within ICD 10 chapter	49.5%	4.2%	4.2%	3.2%	38.9%	100.0%

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	110.290[a]	32	.000
Likelihood Ratio	45.360	32	**.059**
Linear-by-Linear Association	.127	1	.721
N of Valid Cases	95		

a. 41 cells (91.1%) have expected count less than 5. The minimum expected count is .06.

Symmetric Measures

		Value	Approximate Significance
Nominal by Nominal	Phi	1.077	.000
	Cramer's V	.539	.000
N of Valid Cases		95	

APPENDIX IV

- Supplementary Table 1. Excluded articles from V4 musculoskeletal disease search results (Chapter VIII).

Author	Year	Title	Reference	Doi
Kawalec P	2016	Disease activity, quality of life and indirect costs of psoriatic arthritis in Poland	Rheumatol Int. 2016 Sep;36(9):1223-30	10.1007/s00296-016-3514-3
Mattila K	2015	Influence of rheumatoid arthritis-related morning stiffness on productivity at work: results from a survey in 11 European countries	Rheumatol Int. 2015 Nov;35(11):1791-7	10.1007/s00296-015-3275-4
Lambert J	2014	Linguistic validation into 20 languages and content validity of the rheumatoid arthritis-specific Work Productivity and Activity Impairment questionnaire	Patient. 2014;7(2):171-6	10.1007/s40271-014-0053-4
Gajšek B	2020	The impact of the applied technology on health and productivity in manual "picker-to-part" systems	Work. 2020;65(3):525-536. doi: 10.3233/WOR-203107.	10.3233/WOR-203107
Tužil J	2020	Short-term response in new users of anti-TNF predicts long-term productivity and non-disability: analysis of Czech ATTRA ankylosing spondylitis biologic registry	Expert Opin Biol Ther. 2020 Feb;20(2):183-192. doi: 10.1080/14712598.2020.1694900. Epub 2019 Nov 25.	10.1080/14712598.2020.1694900
Steffl M	2017	The increase in health care costs associated with muscle weakness in older people without long-term illnesses in the Czech Republic: results from the Survey of Health, Ageing and Retirement in Europe (SHARE)	Clin Interv Aging. 2017 Nov 27;12:2003-2007. doi: 10.2147/CIA.S150826. eCollection 2017.	10.2147/CIA.S150826
Wei JC	2018	Efficacy and safety of etanercept in patients from Latin America, Central Europe and Asia with early non-radiographic axial spondyloarthritis	Int J Rheum Dis. 2018 Jul;21(7):1443-1451. doi: 10.1111/1756-185X.12973. Epub 2016 Nov 11.	10.1111/1756-185X.12973
Cavazza M	2016	Social/economic costs and health-related quality of life in patients with Duchenne muscular dystrophy in Europe	Eur J Health Econ. 2016 Apr;17 Suppl 1:19-29. doi: 10.1007/s10198-016-0782-5. Epub 2016 Apr 2.	10.1007/s10198-016-0782-5

Dias J	2013	Surgical management of Dupuytren's contracture in Europe: regional analysis of a surgeon survey and patient chart review	Int J Clin Pract. 2013 Mar;67(3):271-81. doi: 10.1111/ijcp.12106.	10.1111/ijcp.12106
Horváth G	2010	Prevalence of low back pain and lumbar spine degenerative disorders. Questionnaire survey and clinical-radiological analysis of a representative Hungarian population	Int Orthop. 2010 Dec;34(8):1245-9. doi: 10.1007/s00264-009-0920-0. Epub 2009 Dec 8.	10.1007/s00264-009-0920-0

- Supplementary tables 2. Explorative statistics of normalised 2020 costs

Descriptives

			Statistic	Std. Error
Cost inflated to 2020 Euros	Mean		1787.8725	379.70435
	95% Confidence Interval for Mean	Lower Bound	1004.2013	
		Upper Bound	2571.5438	
	5% Trimmed Mean		1617.3208	
	Median		1191.7356	
	Variance		3604384.743	
	Std. Deviation		1898.52173	
	Minimum		21.75	
	Maximum		6637.37	
	Range		6615.62	
	Interquartile Range		2321.93	
	Skewness		**1.434**	.464
	Kurtosis		1.574	.902

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Cost inflated to 2020 Euros	.176	25	.044	.824	25	**.001**

a. Lilliefors Significance Correction

- Explorative statistics of transformed PL costs (i.e.Log_2020_cost)

Descriptives

			Statistic	Std. Error
Log_Cost_2020	Mean		2.9242	.13075
	95% Confidence Interval for Mean	Lower Bound	2.6544	
		Upper Bound	3.1941	
	5% Trimmed Mean		2.9577	
	Median		3.0762	
	Variance		.427	
	Std. Deviation		.65373	
	Minimum		1.34	
	Maximum		3.82	
	Range		2.48	
	Interquartile Range		1.04	
	Skewness		-.731	.464
	Kurtosis		-.062	.902

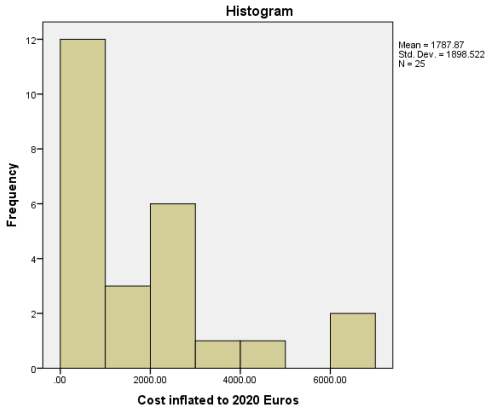
Tests of Normality

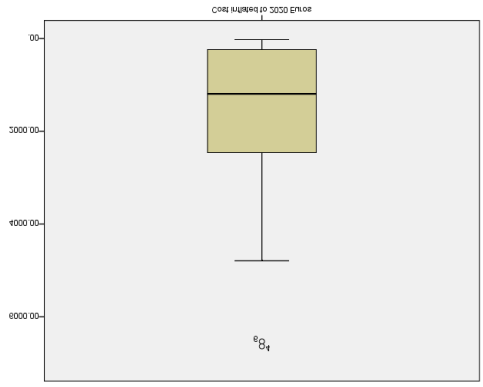
	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Log_Cost_2020	.129	25	.200*	.944	25	.187

*. This is a lower bound of the true significance.

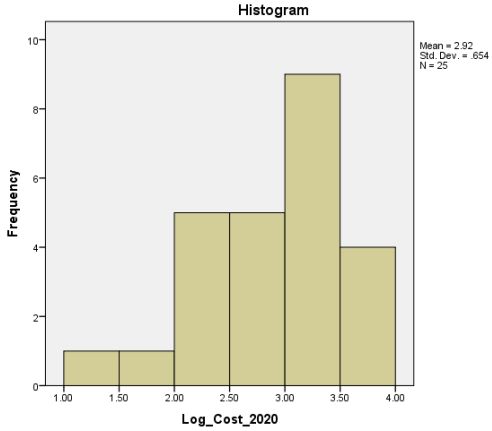
a. Lilliefors Significance Correction

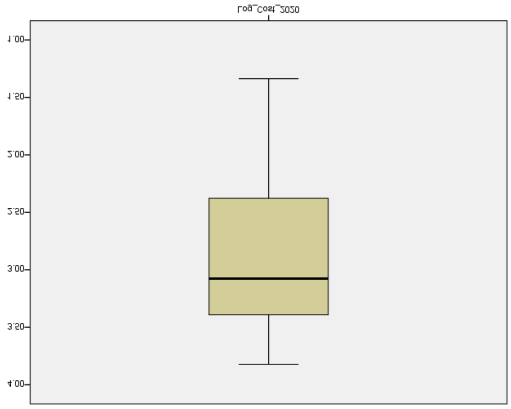
- Costs distribution and box plot before logarithmic transformation:





- Costs distribution and box plot after logarithmic transformation:





- Between country ANOVA analysis results:

Descriptives

Log_Cost_2020

	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
Hungary	10	2.8817	.91399	.28903	2.2279	3.5355	1.34	3.82
Poland	15	2.9526	.43981	.11356	2.7090	3.1961	2.17	3.68
Total	25	2.9242	.65373	.13075	2.6544	3.1941	1.34	3.82

Test of Homogeneity of Variances

Log_Cost_2020

Levene Statistic	df1	df2	Sig.
14.650	1	23	**.001**

ANOVA

Log_Cost_2020

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	.030	1	.030	.068	**.797**
Within Groups	10.226	23	.445		
Total	10.257	24			

Robust Tests of Equality of Means

Log_Cost_2020

	Statistic[a]	df1	df2	Sig.
Brown-Forsythe	.052	1	11.812	**.823**

a. Asymptotically F distributed.

Paired samples t-test normality assumption test for MADs

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
Pair difference	Statistic	df	Sig.	Statistic	df	Sig.
Diff_MAD3_MAD1	.276	6	.172	.860	6	**.190**
Diff_MAD3_MAD2	.295	6	.110	.823	6	**.093**
Diff_MAD3_MAD4	.267	6	.200*	.878	6	**.259**
Diff_MAD3_MAD5	.291	6	.123	.824	6	**.096**

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

Tests of Normality

	Kolmogorov-Smirnova			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Diff_MAD5_MAD2	.306	6	.082	.805	6	**.066**
Diff_MAD5_MAD3	.291	6	.123	.824	6	**.096**
Diff_MAD2_MAD3	.295	6	.110	.823	6	**.093**

a. Lilliefors Significance Correction