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Economic Evaluation

Productivity Loss in Patients With Chronic Diseases: A Pooled Economic Analysis of Hungarian Cost-of-Illness Studies

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ABSTRACT

Objectives: To assess productivity loss (PL) variations across a set of chronic diseases and analyze significant PL drivers (demographics, health status, healthcare resource use) in Hungary.

Methods: Data from 11 cost-of-illness studies (psoriasis, dementia, systemic sclerosis, multiple sclerosis, benign prostatic hyperplasia, Parkinson's disease, psoriatic arthritis, rheumatoid arthritis, schizophrenia, epilepsy, and diabetes) were pooled, and patient-level data were analyzed. A weighted multiple linear regression analysis was run to identify significant PL indicators. All costs were adjusted to 2018 euro rates and PL was further presented as a proportion of gross domestic product/capita, facilitating results comparability and transferability.

Results: The dataset comprised 1888 patients from 11 chronic diseases. The average indirect cost/(gross domestic product/capita) ratio was highest in schizophrenia (72.4%) and rheumatoid arthritis (71.3%) and lowest in benign prostatic hyperplasia (1.6%). Correlation results infer that a higher EuroQol 5-dimension 3-level index score was significantly associated with lower PL. The number of hospital admissions was the main contributor toward increasing PL among resource use indicators. Age and sex showed inconsistent and insignificant correlations with PL. In regression analysis, a better EuroQol 5-dimension 3-level index score and higher education were consistently associated with decreasing PL in all models.

Conclusions: This article will enable health decision makers to understand the importance of adopting a societal perspective for chronic disease reimbursement decisions. The correlation between PL and health status supports that timely started effective treatments may prevent patients from losing their workability.

Keywords: benign prostatic hyperplasia, diabetes, dementia, epilepsy, Hungary, productivity loss, indirect cost, multiple sclerosis, psoriasis, systemic sclerosis, Parkinson's disease, psoriatic arthritis, rheumatoid arthritis, schizophrenia.

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Introduction

As a basic term, productivity is simply a measure of output per unit of input. For health professionals, the term productivity loss (PL) is defined as the output loss due to health issues corresponding to reduced work output by the productive person, whether paid or unpaid.[1] Direct treatment costs of chronic diseases are rapidly increasing and are only expected to keep increasing with the continuous development of the new costly yet effective biologic agents.[2] This has been placing an increasing pressure on policy makers to reimburse the most socially sustainable health interventions. Therefore, considerable attention to the adoption of a societal perspective in health economic evaluations is starting to emerge.[3] Although a societal perspective in health economic evaluation is often not mandatory, the inclusion of such costs into health economic evaluations can maximize social welfare in the long run.[4] In 2016, The Netherlands released its updated pharmacoeconomic guidelines mandating the conduction of health economic analysis from a societal perspective. These guidelines also go further to specify the use of friction cost as the prescribed productivity cost estimation method.[5,6] More countries are expected to imitate The Netherlands' pharmacoeconomic guidelines and start mandating a societal perspective in health economic evaluations.

One prevalent issue in PL evaluations is the weak international transferability of the results owing to the fragile standardization of current indirect costs reporting methodologies. Knies et al[7] investigated the weak PL transferability issue and found that the

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Table 1. Characteristics of the included COI studies: language, costing year, PL methods, gross income, and wage rate.

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	9	English	2014	WPAI	Yes	HCA	989	95.6
Dementia	10	English	2007	Open question	No	HCA	993	96.0
Diabetes	11	Hungarian	2003	Open question	No	HCA	653	63.1
Epilepsy	12	Hungarian	2009	Open question	No	HCA	957	92.5
Multiple sclerosis	13	English	2009	Open question	No	HCA	957	92.5
Parkinson's disease	14	English	2009	Open question	No	HCA	957	92.5
Psoriasis	15	English	2012	WPAI	No	Both	1054	101.9
Psoriatic arthritis	8	English	2007	Open question	No	HCA	996	96.3
Rheumatoid arthritis	16	English	2004	Open question	No	HCA	490	47.4
Schizophrenia	17	Hungarian	2009	Open question	No	HCA	957	92.5
Systemic sclerosis	18	English	2006	Open question	No	HCA	913	88.3

FCA indicates friction cost approach; HCA, human capital approach; WPAI, Work Productivity and Activity Impairment.
*Average nominal gross wage in 2018 in Hungary was 1034.5 euros (Source: Hungarian Statistical Office website[23]).

complication starts from the absence of international consensus on the inclusion of the societal perspective in health economic evaluations. Moreover, whenever a societal perspective is to be adopted, differences in PL measurement and valuation methods further contribute to the results transferability complexity. For example, either costs or quality-adjusted life-years are usually adopted for PL valuation; this alone imposes a major hurdle on results transferability and could result in many complications and errors, such as double counting when converting the results between costs and quality-adjusted life-years and vice versa.

The objective of this article is to assess the PL variations across a set of chronic diseases and analyze PL drivers (demographics, health status, healthcare resource use) in Hungarian patients. Such economic analysis can aid health policy makers in visualizing the PL impact on chronic disease patients, by directly demonstrating the monetary value of adopting a societal perspective for reimbursement decisions. Moreover, to enhance the transferability of our findings, all costs were calculated and presented in unified, adjusted monetary terms (ie, PL as a percentage of gross domestic product [GDP]/capita in 2018), facilitating comparison with similar international cost-of-illness (COI) studies.

Methods

Data Sources and Tools

This study uses data from 11 noninterventional, cross-sectional, retrospective COI studies conducted in different medical centers in Hungary between 2003 and 2015. Our analysis encompassed the following 11 chronic diseases: psoriatic

Table 2. Disease-specific demographics, resource use, health status, adjusted indirect cost, and indirect cost as a percent of total cost.

Disease name	Total number of patients	Number of patients below 64	Age mean (95% CI)	Higher education patients N (%)	Female N (%)	EQ-5D-3L index (95% CI)	Disease duration in years (95% CI)
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)
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)
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)
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)
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)
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)
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)
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)
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)
Schizophrenia	78	73	44.24 (41.30-47.19)	9 (12%)	36 (46.2)	0.64 (0.57-0.71)	N/A*
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)
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)

arthritis,[8] benign prostatic hyperplasia (BPH),[9] dementia,[10] diabetes,[11] epilepsy,[12] multiple sclerosis,[13] Parkinson's disease,[14] psoriasis,[15] rheumatoid arthritis,[16] schizophrenia,[17] and systemic sclerosis.[18] 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 caregivers in case of dementia) by the department of health economics at Corvinus University of Budapest, and were later combined for this work. EuroQol 5-dimension 3-level (EQ-5D-3L) index scores were measured using the validated Hungarian version. The EQ-5D-3L is a group of instruments used to provide a perception of health state, has been used and validated in many disease areas over the past 30 years,[19] and is the health status tool of choice recommended by many health technology assessment organizations.[20] Local ethical approvals were obtained if the COI was conducted in a single institution, while national ethical approval was acquired in case the study was conducted in different medical centers within the country. All patients signed an informed consent form. Specific information on each included COI study, such as costing year, gross wage, productivity loss measurement method (Work Productivity and Activity Impairment [WPAI] or open question), and the adopted costing approach (ie, human capital or friction cost) were extracted by the authors from the relevant publications. The WPAI questionnaire is an instrument developed to measure a patient's impairment owing to a health condition, for both paid (absenteeism and presenteeism) and unpaid work.[21] The human capital approach (HCA) and the friction cost approach are the 2 dominating methods used for the valuation of PL in paid work and are preferred given their simple, direct monetary results. Both methods have specific limitations and advantages and are discussed elsewhere.[22]

Costing

Cost-of-illness calculations were performed from a societal perspective (including direct medical, direct nonmedical, and indirect costs). All COI studies applied similar methods to measure time off work and resource use. Patients (or caregivers in dementia) were asked about sick leaves and their employment status, including whether they were entitled to disability pension owing to the disease. 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 by dividing the average gross wage for 2018 by the average gross wage for the study year to obtain a specific conversion factor, which was then multiplied with the corresponding disease indirect cost to obtain the adjusted PL costs in unified 2018 euro rates. Furthermore, indirect costs were expressed as a percentage of GDP per capita for 2018 (indirect costs[GDP/capita]) by dividing each disease's adjusted indirect cost by the national GDP/capita in Hungary for 2018. The average national gross wage in Hungary for 2018 was acquired from the Hungarian Central Statistical Office website,[23] which amounted to Hungarian forint 329 900 = 1034.5 euros (318.9 Hungarian forint = 1 euro). Similarly, the 2018 Hungarian GDP/capita (13 686 euros) was obtained from the Hungarian Central Statistical Office website.[24]

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 4 categories: PL variables (ie, number of missed working hours and indirect costs), demographic variables (ie, age, sex, and education level), resource use variables (ie, number of general practitioner [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 any specific disease and PL. To measure the sex (male/female), educational level (university degree/no university degree), and informal care (received/did not receive) impact on PL, analysis of variance was used to compare disease group means of lost productive hours for each subgroup, whereas Spearman's rho was employed to identify significant correlations between resource use, health status, and age variables and PL.

Weighted linear regression analysis was also run to identify significant PL indicators and construct a predictive model for PL in chronic disease patients in Hungary. A weighting variable was calculated to account for the differences in the sample size

Table 2. Continued

Number of outpatient visits mean (95% CI)	Number of GP visits mean (95% CI)	Number of hospital admission mean (95% CI)	Number of missed working hours per year mean (95% CI)	Adjusted indirect cost in euros (2018 rates)	Indirect cost as a percent of total cost
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)	23.2
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)	15.0
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)	46.1
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)	49.1
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)	20.6
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)	34.9
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)	14.1
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)	52.1
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)	67.4
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)	66.1
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)	56.0
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)	43.3

EQ-5D-3L indicates EuroQol 5-dimension 3-level index; GP, general practitioner.
*N/A: Data missing from the original database.

Table 3. Disease-specific relationship of PL (hours lost/year) with demographics, resource use, and health status indicators.

Disease name	Correlation with lost productive hours					
	GP visit	Hospital admissions	Outpatient visits	EQ-5D-3L index	Age (all)	Age (<64)
	Spearman's rho (P)					
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)
Dementia	−0.001 (0.990)	**0.275 (0.010)**	0.082 (0.447)	−0.074 (0.495)	0.118 (0.276)	N/A*
Diabetes	0.040 (0.416)	N/A	−0.085 (0.064)	**−0.232 (0.000)**	0.001 (0.985)	**0.133 (0.014)**
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)**
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)
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)**
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)
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)
Rheumatoid arthritis	**0.255 (0.000)**	**0.124 (0.049)**	0.116 (0.068)	**−0.131 (0.040)**	**−0.401 (0.000)**	−0.132 (0.073)
Schizophrenia	−0.035 (0.761)	N/A	0.054 (0.639)	**−0.226 (0.046)**	0.110 (0.340)	**0.424 (0.000)**
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)

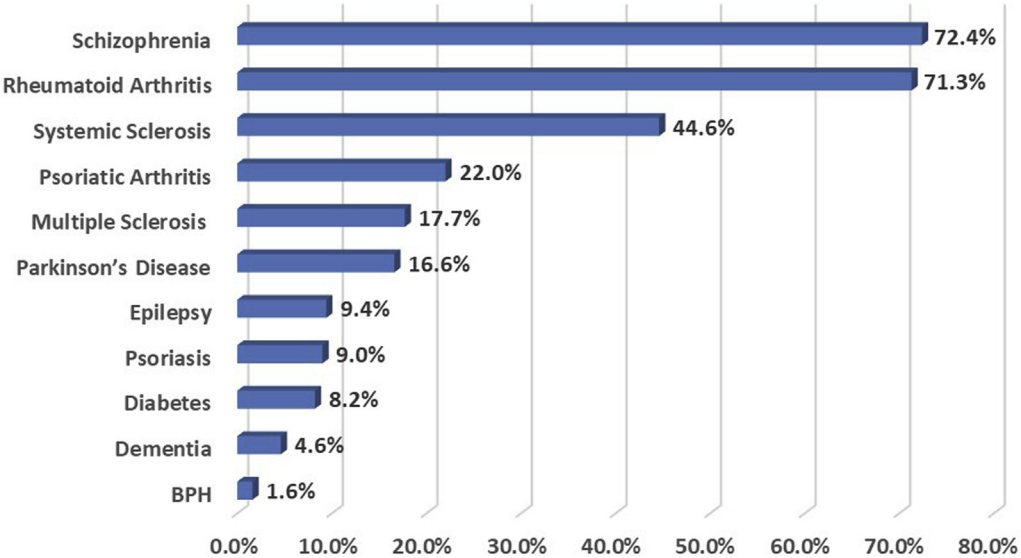
between diseases, by dividing 100 by the number of patients in each disease group to obtain a disease-specific value. The resulting weight value for each disease was then incorporated into our models as the regression weighting variable, omitting the effect of sample size in our models. Owing to some missing information in our database; 4 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 among the 4 models is as follows: the first 2 models (models 1 and 2) included all the 1 disease populations with the following independent variables—age, disease duration, EQ-5D-3L index, sex, number of GP visits, and number of outpatient visits—whereas the latter 2 models (models 3 and 4) excluded diabetes patients while using 2 additional independent variables (ie, 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,[25] simulating the working population within our sample.

Results

Characteristics of Studies

Three of the 11 COI studies were published in Hungarian language and 8 in English. Patient sample sizes ranged between 68 (multiple sclerosis) and 480 (diabetes), whereas the total population comprised 1888 patients, including 1222 patients who were of working age (under 64). The predominant productivity valuation approach adopted was the HCA, with 1 article using both HCA and friction cost approach together. For all 11 studies, 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 2 COI studies using the WPAI

Figure 1. Indirect cost per patient as a percentage of (GDP/capita) for each investigated chronic disease.



BPH indicates benign prostatic hyperplasia.

Table 3. Continued

Sex		Education		Informal care	
Female (male)	*P*	Higher (lower)	*P*	Received (did not receive)	*P*
Lost hours mean	ANOVA	Lost hours mean	ANOVA	N (%)	ANOVA
N/A 35.67	N/A	**78.71 (17.25)**	**0.050**	0.0 (38.15)	0.513
136.88 (59.76)	0.327	26.50 (116.99)	0.416	120.83 (13.35)	0.358
131.17 (259.12)	**0.012**	N/A	N/A	N/A	N/A
282.62 (121.52)	**0.046**	64.94 (247.89)	0.079	**739.62 (118.55)**	**0.000**
416.13 (380.36)	0.858	250.33 (474.17)	0.211	**856.11 (143.69)**	**0.000**
366.97 (385.72)	0.911	277.38 (440.53)	0.315	522.24 (254.76)	0.086
315.07 (155.25)	0.065	85.52 (236.61))	0.135	227.38 (204.19)	0.867
526.24 (476.89)	0.700	410.30 (537.79)	0.394	**731.76 (368.08)**	**0.005**
1629.39 (1726.37)	0.788	**522.51 (1879.07)**	**0.000**	1763.58 (1510.80)	0.314
1646.23 (1670.99)	0.895	**1155.25 (1725.34)**	**0.049**	1819.52 (1588.47)	0.253
1077.39 (533.73)	0.165	993.62 (1030.37)	0.901	1131.18 (954.60)	0.466

Note. Significant variables in bold font. N/A, data missing from the original database.
ANOVA indicates analysis of variance; EQ-5D-3L, EuroQol 5-dimension 3-level index; GP, general practitioner.
*Only 6 patients are under 64. Spearman correlation could not be performed.

questionnaire. The characteristics of the investigated COI studies are summarized in Table 1.

Descriptive Results by Disease

Table 2 summarizes the demographics, health status, and healthcare 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 the 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 1660 lost hours per patient, followed closely by musculoskeletal diseases (ie, rheumatoid arthritis and systemic sclerosis). Benign prostatic hyperplasia, 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 (9912 euros) followed closely by rheumatoid arthritis, whereas 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, but lowest in BPH. Lost productive hours and cost means are summarized in Table 2, and Figure 1 shows a bar chart of indirect cost as a percentage of GDP/capita for each investigated chronic disease.

Determinants of PL

Table 3 shows the association of PL with demographic, resource use, and health status variables. Analysis of variance of disease PL means revealed that sex differences were significant only in diabetes and epilepsy, whereas higher education levels resulted in significant PL in patients with BPH, rheumatoid arthritis, and schizophrenia. In resource use, we found that a higher number of hospital admissions significantly increases PL in BPH, dementia, multiple sclerosis, Parkinson's disease, psoriasis, psoriatic arthritis, and rheumatoid arthritis patients, but 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 not significant differences were observed in all other diseases for informal care use. Overall, resource use variables, where significant, correlated positively toward 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, but they correlated negatively with Parkinson's disease patients (owing 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 it correlated negatively with BPH, Parkinson's disease, psoriatic arthritis, and rheumatoid arthritis patients.

Weighted Regression Modeling

Four predictive models were constructed with resulting R squared values of 0.354, 0.404, 0.367, and 0.420 for models 1 through 4, respectively. The resulting unstandardized beta coefficients and their corresponding significance for our models are presented in Table 4. 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

Table 4. Weighted linear regression models 1 through 4.

Linear regression	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
Sex	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**	

Note. Variables unstandardized B coefficients and their corresponding significance values. BPH was used as the reference variable for all models (lowest indirect cost). Significant variables are in bold font. Results are significant at $P < .005$.
BPH indicates benign prostatic hyperplasia; EQ-5D-3L, EuroQol 5-dimension 3-level index; GP, general practitioner.

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, whereas 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 utilization, 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 utilization, 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.

Discussion

In 2012, the World Health Organization announced chronic diseases as one of the major challenges facing nations worldwide in the current century.[26,27] This article presents the largest set of chronic disease indirect cost results in the Central and Eastern Europe region. Productivity loss data from 11 COI studies have been pooled, adjusted, and compared to reflect each disease's current total and indirect cost estimates, and were further presented using internationally transferrable monetary terms. Significant healthcare resource use, health status, and demographic variables driving PL in chronic disease patients were also identified and quantified. 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.[28] It is mandatory for all citizens living in Hungary to take the national health insurance; however, private insurance policies can be bought as well.[29] The current Hungarian health economic guideline recommends the analysis to be conducted from the healthcare system perspective, and later mentions that a societal perspective is only optional.[30]

Our PL correlation results infer that a better health status score was the only indicator with a consistent negative impact on PL (although not always significant). On the other hand, in resource use, the number of hospital admissions was the highest

contributor toward 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 (ie, 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 sex PL means was apparent in most diseases, it was inconsistent for a specific sex (eg, diabetes and epilepsy).

Regression modeling revealed that only health status score (ie, ED-5D-3L) had a consistent, significant negative impact on PL (decreasing lost productive hours) across all 4 models. Similarly, in models where education level was accounted for (ie, models 3, 4), a significant decrease in PL was observed with higher educational levels. This was addressed by Zimmerman et al,[31] who investigated higher education impact on overall health and proposed a hypothesis that adults with relatively higher levels of education tend to have greater socioeconomic 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 the role of sex in PL modeling, none of our 4 predictive models flagged sex as a significant PL variable. Rather, the main contributor in all of our 4 models was being a patient of 1 of the 3 most cost-intensive diseases (ie, schizophrenia and musculoskeletal diseases).

As demonstrated in our article, indirect costs can comprise a large chunk of the total economic burden of chronic diseases. Health policy makers often disregard indirect costs for 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 evaluations further imposes more challenges. 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.[32] Devising one universal reporting method for all diseases can be farfetched given the diverse nature of diseases. One the other hand, proposals for the standardization of COI reporting methodologies for a specific disease, although still scarce, are starting to emerge. Jin and Mosweu,[33] 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 analyzed 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 employed in health economic evaluations,[34,35] this measure has proven to be inadequate to facilitate the international transferability of results. For instance, Jin and Mosweu,[33] who extracted this ratio for schizophrenia from multiple COI studies, 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[36] to up to 83% in South Korea as reported by Chang et al.[37] While our costs for schizophrenia resulted in 66% indirect cost proportion from total cost. Similarly, Blahova et al[38] published a COI study for multiple sclerosis costs in the Czech Republic with a resulting proportion of 45% indirect costs out of total costs compared with 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 this 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) utilization, a 3-level categorization system is proposed; high PL (above 50%), moderate PL (15%-50%), and low PL (below 15%). To give perspective, 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, whereas dementia, diabetes, epilepsy, psoriasis, and BPH patients fell into the low PL category. In a similar methodological approach, Zhao et al[39] conducted a cross-country secondary analysis for the COI studies that 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 quantitatively synthesized so that the indirect costs are presented as a percentage of the national gross domestic product per capita "indirect cost/(GDP/capita)." Three different indirect cost/(GDP/capita) means (95% CI) were reported (ie, 66.5% (66.0-67.0), 79.2% (54.0-104.3), and 79.2% (52.4-117.8), based on 3 modeling approaches (ie, fixed-effect model, random-effect model, and bootstrapping estimation), respectively. All 3 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 PL results transferability.

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

Conclusion

Results of our study provide useful monetary insights on PL impact and drivers in chronic disease patients in Hungary. This article will enable health decision makers to understand the importance of adopting a societal perspective for chronic disease reimbursement decisions. The significant correlation between PL and health status (ie, EQ-5D-3L index) supports that timely started effective treatments may prevent people from losing their workability. Schizophrenia and musculoskeletal disease patients had the highest PL, whereas BPH patients' PL was the lowest. We also demonstrated that indirect costs (GDP/capita) can enhance the international PL comparability and transferability.

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REFERENCES

1. Zhang W, Bansback N, Anis AH. Measuring and valuing productivity loss due to poor health: a critical review. *Soc Sci Med*. 2011;72(2):185–192.
2. Cheng J, Feldman SR. The cost of biologics for psoriasis is increasing. *Drugs Context*. 2014;17(3):212266.
3. Brennan P, Perola M, van Ommen G-J, Riboli E, Consortium EC. Chronic disease research in Europe and the need for integrated population cohorts. *Eur J Epidemiol*. 2017;32(9):741–749.
4. Krol M, Brouwer W. How to estimate productivity costs in economic evaluations. *Pharmacoeconomics*. 2014;32(4):335–344.
5. Versteegh M, Knies S, Brouwer W. From good to better: new Dutch guidelines for economic evaluations in healthcare. *Pharmacoeconomics*. 2016;34(11):1071–1074.
6. Koopmanschap MA, Rutten FF, van Ineveld BM, Van Roijen L. The friction cost method for measuring indirect costs of disease. *J Health Econ*. 1995;14(2):171–189.
7. Knies S, Severens JL, Ament AJ, Evers SM. The transferability of valuing lost productivity across jurisdictions. Differences between national pharmacoeconomic guidelines. *Value Health*. 2010;13(5):519–527.
8. Brodszky V, Bálint P, Géher P, et al. Disease burden of psoriatic arthritis compared to rheumatoid arthritis, Hungarian experiment. *Rheumatol Int*. 2009;30(2):199–205.
9. Rencz F, Kovács Á, Brodszky V, et al. Cost of illness of medically treated benign prostatic hyperplasia in Hungary. *Int Urol Nephrol*. 2015;47(8):1241–1249.
10. Érsek K, Kovács T, Wimo A, et al. Costs of dementia in Hungary. *J Nutr Health Aging*. 2010;14(8):633–639.
11. Jermendy G, Gaál Z, Gerő L, et al. Egészségügyi szakmai irányelv—a diabetes mellitus kórismézéséről, a cukorbetegek antihyperglykaemiás kezeléséről és gondozásáról felnőttkorban. *Diabetol Hung*. 2017;25:3–77.
12. Pentek M, Bereczki D, Gulacsi L, et al. Survey of adults living with epilepsy in Hungary: health-related quality of life and costs. *Ideggyogy Sz*. 2013;66(7-8):251–261.
13. Pentek M, Gulacsi L, Rozsa C, et al. Health status and costs of ambulatory patients with multiple sclerosis in Hungary. *Ideggyogy Sz*. 2012;65(9-10):316–324.
14. Tamás G, Gulácsi L, Bereczki D, et al. Quality of life and costs in Parkinson's disease: a cross sectional study in Hungary. *PLoS One*. 2014;9(9), e107704.
15. Balogh O, Brodszky V, Gulácsi L, et al. Cost-of-illness in patients with moderate to severe psoriasis: a cross-sectional survey in Hungarian dermatological centres. *Eur J Health Econ*. 2014;15(1):101–109.
16. Péntek M, Kobelt G, Czirják L, et al. Costs of rheumatoid arthritis in Hungary. *J Rheumatol*. 2007;34(6), 1437-1437.
17. Péntek M, Harangozó J, Egerházi A, et al. Health related quality of life and disease burden of patients with schizophrenia in Hungary. *Psychiatr Hung*. 2012;27(1):4–17.
18. Minier T, Péntek M, Brodszky V, et al. Cost-of-illness of patients with systemic sclerosis in a tertiary care centre. *Rheumatology (Oxford)*. 2010;49(10):1920–1928.
19. Devlin NJ, Brooks R. EQ-5D and the EuroQol group: past, present and future. *Appl Health Econ Health Policy*. 2017;15(2):127–137.
20. Mukuria C, Rowen D, Hernández-Alava M, Dixon S, Ara R. Predicting productivity losses from health-related quality of life using patient data. *Appl Health Econ Health Policy*. 2017;15(5):597–614.
21. Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. *Pharmacoeconomics*. 1993;4(5):353–365.
22. Pike J, Grosse SD. Friction cost estimates of productivity costs in cost-of-illness studies in comparison with human capital estimates: a review. *Appl Health Econ Health Policy*. 2018;16(6):765–778.
23. Hungarian Central Statistical Office. Average gross earnings. https://www.ksh.hu/docs/eng/xftp/gyor/ker/eker1812.html. Accessed October 21, 2019.
24. Hungarian Central Statistical Office. Per capita gross domestic product. https://www.ksh.hu/docs/eng/xstadat/xstadat_annual/i_qpt016.html. Accessed October 21, 2019.
25. Simonovits A. The mandatory private pension pillar in Hungary: an obituary. *Int Soc Secur Rev*. 2011;64(3):81–98.
26. Bloom D, Cafiero E, Jané-Llopis E, Abrahams-Gessel S, Bloom L, Fathima S. *The global economic burden of non-communicable diseases report*. The World Economic Forum and the Harvard School of Public Health; 2011.
27. *Third Copenhagen Consensus Outcome Document*. Copenhagen Consensus Center; 2012.
28. Gulácsi L, Brodszky V, Péntek M, Varga S, Vas G, Boncz I. History of health technology assessment in Hungary. *Int J Technol Assess Health Care*. 2009;25(S1):120–126.
29. Nolte E, Knai C, Saltman R. *Assessing Chronic Disease Management in European health Systems: Concepts and Approaches*. World Health Organization; 2015.
30. Szende Á, Mogyorosy Z, Muszbek N, Nagy J, Pallos G, Dózsa C. Methodological guidelines for conducting economic evaluation of healthcare interventions in Hungary: a Hungarian proposal for methodology standards. *Eur J Health Econ*. 2002;3(3):196–206.
31. Zimmerman EB, Woolf SH, Haley A. *Understanding the Relationship Between Education and Health: A Review of the Evidence and an Examination of Community Perspectives*. Rockville, MD: Agency for Healthcare Research and Quality; 2015.
32. Onukwugha E, McRae J, Kravetz A, Varga S, Khairnar R, Mullins CD. Cost-of-illness studies: an updated review of current methods. *Pharmacoeconomics*. 2016;34(1):43–58.
33. Jin H, Mosweu I. The societal cost of schizophrenia: a systematic review. *Pharmacoeconomics*. 2017;35(1):25–42.
34. Thienpont E, Paternostre F, Van Wymeersch C. The indirect cost of patient-specific instruments. *Acta Orthop Belg*. 2015;81(3):462–470.
35. Le KD, Vuong LN, Ho TM, et al. A cost-effectiveness analysis of freeze-only or fresh embryo transfer in IVF of non-PCOS women. *Hum Reprod*. 2018;33(10):1907–1914.
36. Evensen S, Wisløff T, Lystad JU, Bull H, Ueland T, Falkum E. Prevalence, employment rate, and cost of schizophrenia in a high-income welfare society: a population-based study using comprehensive health and welfare registers. *Schizophr Bull*. 2015;42(2):476–483.
37. Chang SM, Cho S-J, Jeon HJ, et al. Economic burden of schizophrenia in South Korea. *J Korean Med Sci*. 2008;23(2):167–175.
38. Blahova Dusankova J, Kalincik T, Dolezal T, Kobelt G, Havrdova E. Cost of multiple sclerosis in the Czech Republic: the COMS study. *Mult Scler*. 2012;18(5):662–668.
39. Zhao F-L, Xie F, Hu H, Li S-C. Transferability of indirect cost of chronic disease: a systematic review and meta-analysis. *Pharmacoeconomics*. 2013;31(6):501–508.