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Review

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Cost-of-illness studies: concepts, scopes, and methods

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Liver diseases are one of the main causes of death, and their ever-increasing prevalence is threatening to cause significant damage both to individuals and society as a whole. This damage is especially serious for the economically active population in Korea. From the societal perspective, it is therefore necessary to consider the economic impacts associated with liver diseases, and identify interventions that can reduce the burden of these diseases. The cost-of-illness study is considered to be an essential evaluation technique in health care. By measuring and comparing the economic burdens of diseases to society, such studies can help health-care decision-makers to set up and prioritize health-care policies and interventions. Using economic theories, this paper introduces various study methods that are generally applicable to most disease cases for estimating the costs of illness associated with mortality, morbidity, disability, and other disease characteristics. It also presents concepts and scopes of costs along with different cost categories from different research perspectives in cost estimations. By discussing the epidemiological and economic grounds of the cost-of-illness study, the reported results represent useful information about several evaluation techniques at an advanced level, such as cost-benefit analysis, cost-effectiveness analysis, and cost-utility analysis. **(Clin Mol Hepatol 2014;20:327-337)**

Keywords: Cost-of-illness study; Burden of disease; Health policies

INTRODUCTION

In most of economic and business decision making processes, private or public, the term 'cost' should always be considered while its counterpart varies from benefit (in cost-benefit analysis, CBA), to effectiveness (in cost-effectiveness analysis, CEA), and especially in healthcare fields, to quality-adjusted life years (QALYs) or latent utility (in cost-utility analysis, CUA). Though sometimes measured in different forms, costs are most commonly measured in monetary terms for a direct comparison among alternative options.

Cost of illness (COI), known as burden of disease (BOD), is a definition that encompasses various aspects of the disease impact on the health outcomes in a country, specific regions, communities, and even individuals. The category of COI can range from the incidence or prevalence of disease to its effect on longevity, morbidity along with the decrease in health status and quality of life (QoL), and financial aspects including direct and indirect expenditures that result from premature death, disability or injury due to corresponding disease and/ or its comorbidities.

Accurate knowledge about COI is essential and helps us formulate and prioritize health care policies and interventions and eventually allocate health care resources in accordance with budget constraints in order to achieve policy efficiency. So, it is crucially

Abbreviations:

BOD, burden of disease; CA, conjoint analysis; CBA, cost-benefit analysis; CEA, cost-effectiveness analysis; CL, conditional logit; COI, cost of illness; CUA, cost-utility analysis; CVM, contingent valuation method; DALY, disability-adjusted life year; DCE, discrete choice experiment; EQ-5D, EuroQol five dimension questionnaire; FCM, friction cost method; HCM, human capital method; HUI, health utilities index; IID, independent and identically distributed; LY, life year; MRS, marginal rate of substitution; MWTP, marginal willingness-to-pay PAF, population-attributable fraction; NHE, national health expenditures; PV, present value; QALY, quality-adjusted life year; QoL, quality of life; WTP, willingness to pay; YLD, years lost to disability; YLL, years of life lost.

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important to understand how the costs are defined, classified and measured in the COI study. In this paper, we would like to deal with the definitions, categories, types of study approaches regarding COI to conclusively position cost analysis as a useful tool for decision making process in healthcare sectors.

In fact, estimates of the COI using various methodologies serve many purposes. Firstly, cost estimates are frequently used to argue that policies on a disease and its related diseases should be given a high priority in a policy agenda setting. The public is entitled to a quality standard against which individual COI studies can be assessed. Without such a standard, the advocates are prone to adding extra items to highlight and frequently exaggerate the COI results. Secondly, cost estimates help appropriately target specific problems and policies. It is important to know whether a specific disease of interest involves the greater medical and/ or social costs. Additionally, the improvement of cost estimates can be a good baseline measure to determine the efficacy of health policies, programs, or any types of interventions that are designed to reduce or eradicate the detrimental disease effects. Estimates of social costs can also facilitate cross-national comparisons of the disease consequences and various approaches that are available to confronting those consequences.

BASIC CONCEPTS OF COI STUDIES

The fundamental goal of COI study is to evaluate the economic burden that illness imposes on society as a whole. As explicitly stated in Jefferson et al. (2000), "the aim of COI studies is descriptive: to itemize, value, and sum the costs of a particular problem with the aim of giving an idea of its economic burden."

So in conducting COI studies, researchers are required to recognize, identify, list, measure and value the costs that a disease and its comorbidities can generate.[1] And Clabaugh and Ward (2008) identify that 'analyzing COI presents useful opportunities for communicating with the public and policy makers on the relative importance of specific diseases and injuries'.[2]

In carrying out COI studies, we need to keep in mind that an underlying assumption is that the economic COI represent the 'potential benefits of a health care intervention' if it had eradicated the illness. In this vein, the COI studies generally include some metric of 'health loss' and try to measure the resource costs incurred in treating the related diseases. The BOD studies specifically measure the 'burden' of years of life lost (YLL) due to premature death, and the years lost due to disability or morbidity (YLD). These two categories make up a measure of 'cost' called total DALYs (disability-adjusted life years), which encompass health care costs and the 'lost economic or societal contribution' resulting from premature death or disability.

TYPES OF COSTS

The COI studies traditionally stratify costs into three categories-direct, indirect, and intangible costs. Since the intangible costs have seldom been quantified in COI studies due to the measurement difficulties and related controversies, here we mainly focus on the first two cost categories. The examples of direct and indirect costs associated with health outcomes are presented in Table 1.

Direct costs

Being incurred by the health system, society, family and individual patient, the direct costs consist of healthcare costs and non-healthcare costs. The former is defined as the medical care expenditures for diagnosis, treatment, and rehabilitation, etc., while the latter is related to the consumption of non- healthcare resources like transportation, household expenditures, relocating, property losses, and informal cares of any kinds. The direct cost estimates associated with chronic diseases are higher than those of acute diseases or communicable diseases on condition that the effective and efficacious treatments and prevention methods are adopted.

Indirect costs

Unlike accounting and most of business disciplines where the 'indirect' costs indicate the supporting and overhead activities that need to be shared among the users, the term 'indirect' in COI studies occasionally refers to productivity losses due to morbidity and mortality, borne by the individual, family, society, or the employer. To avoid any confusion or perplexity readers may have, it has been suggested to substitute the term with 'productivity losses or productivity costs'.[3] In fact, the indirect costs form a part of the social welfare losses due to diseases, while the remaining welfare losses are represented by the losses in healthy time resulting from pain, suffering and grief caused by diseases.[4] Measuring indirect costs will be performed through either one of the three major methods listed below:

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Table 1. Examples of costs associated with health outcomes

Direct health care costs		Direct non-health care costs	Indirect costs
- Institutional inpatient care Hospitalization specialized unit (ICU, CCU) Nursing home Terminal care or Hospice - Institutional outpatient service Clinic and ER - Home health care - Physician services General practitioner (GPs) Specialists - Ancillary services Nurses (RNs, Nursing Aid) Nutritionists Physical therapist Ambulance - Overhead allocated to technology Fixed costs of utilities Space and storage Support services Capital costs (depreciation) Construction of facilities Relocation expenses Device or equipment cost - Variable costs of utilities - Medications (prescription and non-prescription) Drug costs Training in new procedures Dispensing and administration Monitoring	- Devices and applications - Drugs, supplies, devices provided by household - Diagnostic test Imaging Laboratory testing - Treatment services Surgery Consumable supplies, personnel time, equipment Treatment of complications Blood products Oxygen Radiation therapy Special diets - Prevention services Screening space Vaccination, prophylaxis Disease prevention in contacts of known cases - Rehabilitation - Training and education Health education Self-care training for patients Life-support skills for general population	- Social services Counseling Retraining - Program evaluation Monitoring impact of program or technology Data analysis - Repair of property destruction - Legal costs - Transportation costs - Time (searching, traveling, waiting etc.) - Childcare or Housekeeping	- Productivity losses Morbidity Mortality Impairment Jon absenteeism - Foregone leisure time - Time spent by family & visitors attending patient

1) Human capital method

From the economic perspective, the term capital refers to one of the factors of production employed to produce valuable and usable goods or services. The human is the subject to take charge of all economic behaviors including transaction, consumption (mainly in a market of goods), and production (in a market of inputs or factors of production). So, it can be recognized that human capital means one of the production factors or inputs that can generate additional values by employing it into a production process. In economics science, human capital can be classified into two types. Firstly, it is to utilize human as labor force related to production process that is generated by or along with other production factors such as financial capital, land, machinery, natural resources and labor hours. Secondly, the human capital can be viewed as the target of investment through formal and informal education and training that formulate knowledge, skills, competency, and experience that are embodied to an individual. The COI study focuses on the latter definition of human capital, which constitutes the individual's productivity in a society.

The productivity losses associated with morbidity and mortality are the 'market value' of that individual's future contribution to production in a society if s/he had continued to work in full health. So the human capital method (HCM) is designed to estimate the value of human capital as the present value of his or her future earnings under the assumption that we use future earnings as a proxy for future productivity, while in many cases the future earnings do not accurately reflect future production, though. Besides, the method has been criticized due to a strong and controversial assumption that a worker cannot be replaced even if the unemployment rate is significantly high. This method would, in this respect overestimate the value of forgone production.[5-7] Despite the problems listed above, however, the HCM is adopted by most COI researchers.

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2) Friction cost method

As an alternative to HCM, the friction cost method (FCM) estimates the value of human capital when another person from the unemployment pool replaces the present value of a worker's future earnings until the sick or impaired worker returns or is eventually replaced. Hence, the friction cost (initial disruption costs plus training costs) is limited to the illness, injury, or premature death of the short term period defined as 'friction period.' It is presumed that the FCM will estimate a lower cost than the human capital method in the long run. Since the FCM assumes that impairment or premature death will not affect the total productivity following the friction period, it is highly controversial and even paradoxical to jump into the conclusion that illness, injuries, and premature deaths would reduce the total unemployment.[8-10]

3) Willingness to pay method

The willingness to pay (WTP) method measures the amount that an individual is eager to pay in order to reduce the probability of illness or mortality.[11] There are various methods to determine and estimate an individual's WTP such as conducting surveys, examining the extra wages for highly risky jobs, examining the demand for products that leads to greater level of health or safety.[12] They are collectively called 'conjoint analysis (CA)', and the contingent valuation method (CVM) is the most commonly used among CA methods. Through hypothetical survey questions, CVM is designed to elicit utility and finally determine an individual's maximum WTP for some good that usually has no market price. Recently, discrete choice experiment (DCE) method is used more frequently in CA, which provides opportunities for evaluation of process effects and non-health outcomes additional to traditional QALY analysis. The DCE technique is an attribute-based measure of benefit, based on the assumptions that, firstly, alternatives (goods or services) can be described by their characteristics (attributes), and secondly, an individual's valuation (i.e., benefit, utility, satisfaction or preference) depends upon the levels of these attributes. In a DCE study, individual respondents are offered a series of choice sets, and asked to choose in each choice set between two or more alternatives. The choice observed is assumed to reveal an underlying (latent) utility function. The DCE approach combines random utility theory with consumer theory, experimental design theory and econometric analysis.

Given several alternatives of choices, each individual chooses one that leads to the highest level of his/her own utility. A random utility model of the consumer choice can be described as below

$$U_{ij} = V_{ij} + \mathcal{E}_{ij} \quad (1)$$

where U_{ij} represents the indirect utility function of individual for good j, V_{ij} deterministic component (defined over levels of attributes and observed characteristics) and $\mathcal{E}_{ij}$ reflects the unobservable factors. An individual i will choose j over other alternative of k if

$$V_{ij} + \mathcal{E}_{ij} > V_{ik} + \mathcal{E}_{ik} \text{ or } V_{ij} - V_{ik} > \mathcal{E}_{ik} - \mathcal{E}_{ij} \quad (2)$$

Given that error terms are unknown, the probability of individual's choice of alternative j can be shown as below

$$\Pr[U_{ij} > U_{ik}] = \Pr[\mathcal{E}_{ik} - \mathcal{E}_{ij} < V_{ij} - V_{ik}] \quad (3)$$

For the empirical purpose, we assume that the deterministic component part of indirect utility function is an additive linear function of several types of attributes and observed characteristics written as $V_{ij} = \beta' X$. Note that a vector of is defined over attributes and observable characteristics and β will be empirically estimated.

Given the distribution of individual error terms, several types of DCE method can be employed depending on the form of the choice model. Among many possible ways, the most widely used discrete choice model is McFadden's conditional logit (CL) model (McFadden, 1974) which is often known as multinomial logit model.[13] In this model, we impose individual error terms as Weibull distributions which are independent and identically distributed (IID). The probability that an individual i makes choice of j among k alternatives can be expressed as below

$$P_{ij} = \frac{\exp(V_{ij})}{\sum_{k=1}^{K} \exp(V_{ik})} \quad (4)$$

where $V_{ij} = \beta' X$. Here, a vector of X represents attributes and observed individual characteristics. The inclusion of individual characteristics (or socio-economic components) in the estimation leads to a 'Hybrid' conditional logit models.[14]

Based on the estimated coefficients from Hybrid CL, the marginal willingness-to-pay (MWTP) can be calculated by computing the marginal rate of substitution (MRS) between attribute of interest and the cost factor (*i.e.* taking the total derivative of the utility index). This 'value ratio' is also identifiable between non-monetary elements of utility.[15]

4) Advantages and limitations of the three methods

A major criticism of the HCM is that depending upon current socioeconomic status, certain groups are assigned a higher value

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than others, which may cause a statistical bias that leads to spurious estimation results.[11,16,17] The WTP approach, usually with higher estimates of the value of life than the HCM attempts to ameliorate these problems.[12] However, this approach is often difficult to implement in COI studies. For specific diseases, we need to perform extensive surveys such as CVM or DCE to elicit people's preferences, although the results heavily depend on people's responses to specific hypothetical questions about their willingness to avoid certain illnesses. And respondents are not able to easily identify the differences in numeric values provided in attributes so that occasionally results in self-selection bias depending upon the severity of the disease or respondents' economic conditions.[18]

People who support the FCM usually criticize the HCM for overvaluing the indirect costs, claiming that the productivity losses are often eliminated after a new employee is well-trained enough to replace the former sick or impaired one. However, the FCM is rarely used because it requires extensive data to estimate only the losses during the friction period. And when firms use their reserved labor inputs to replace impaired workers during the friction period, it will be far more difficult to calculate the productivity losses.[19,20]

With the potential for a wide and drastic variation of indirect costs, it should be clear which method is adopted to estimate indirect costs along with the impact of indirect costs on the total COI. It has been commonly understood that 'COI studies employ varied approaches and many articles have methodological limitations. Without well-accepted standards to guide researchers in their execution of these studies, policymakers and the general public must be wary of the methods used in their calculation and subsequent results.'[2] Besides, the COI methodology has been criticized for several reasons; firstly, it takes into account only the costs of resources but not the utility gain that occurs when reducing the illness.

Secondly, the approach does not compare alternative uses of resources so that it fails to measure and present the opportunity costs adequately.[16,17]

MEASURING BURDEN OF DISEASE

Health outcomes are typically quantified using measures of mortality (YLL) or morbidity (YLD or loss of QoL). The QALYs and DALYs are two common measures that combine and standardize outcomes.

QALYs tend to be used to illustrate health benefits. They are life years adjusted by a quality weight, which is measured on a preference scale, usually a utility scale, where 'full health' equals a score of 1.0, being 'dead' a score of 0.0, and states worse than being dead can have negative scores. In determining the social preferences for utility values, there are various methods adopted such as the standard gamble, the person trade-off, the time trade-off, Health Utilities Index (HUI), EQ-5D, and quality of well-being.

For example, if a person lives for 10 years in full health, and another 10 years in a health state with a quality weight of 0.5, then followed by death, the individual would have achieved $10\times1.0+10\times0.5+0=15$ QALYs. Now suppose with a new treatment adopted, the same person could live for 10 years in full health, 6 years in a health state valued at 0.7, 6 years in a state valued at 0.5, followed by death. In this scenario, s/he would have achieved $10\times1.0+6\times0.7+6\times0.5+0=17.2$ QALYs. Note that although the treatment produced only 2.0 additional life years (LYs) from 20 to 22 years of survival, it created 2.2 additional QALYs (It is practically normal to discount the future years by an appropriate discount rate, while just for convenience sake, it was ignored in this example). It is worth noting that QALYs gained capture the changes in both quantity and quality of life, and the number will be different from the number of LYs gained.

The DALY is a utility measure that means the loss of one year of healthy life, so illustrates the negative impact of a condition. DALYs are commonly used to quantify the burden of disease at a population level. A DALY is a summation of two other health gap indicators: YLL that measures the social burden of fatal health outcomes and YLD that estimates non-fatal outcomes. These two measures take into account the burden of both fatal and non-fatal disease states.

SEVERAL APPROACHES OF COI STUDIES

Prevalence- vs. incidence-based approaches

The COI studies can be described as prevalence-based or incidence-based approaches based on the way in which the epidemiological data are used. Being most commonly used, the former approach estimates the economic burden of a condition over a specific period, usually a year, while the latter approach estimates the lifetime costs of a condition from its onset until its disappearance (usually by cure or death), which refers to the new number of cases arising in a predefined time period. Prevalence-based studies estimate the number of cases of death and hospitalizations attributable to diseases in a given year and then estimate the costs that flow from those deaths or hospitalizations (plus other costs

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such as prevention, research and law enforcement costs). Incidence-based studies estimate the number of new cases of death or hospitalization in a given year and apply a lifetime cost estimate to these new cases.

With the nature of long-lasting conditions such as a long duration that requires considerably lengthy follow-up periods, the prevalence-based approach is the only practicable way to measure the long-term conditions.[1] But it may not quantify the long-term consequences of the conditions.[21] Thus, the prevalence- based approach generally measures the COI in the present and the past in a given year, while incidence-based studies generally estimate the present and future COI in a given year. For ongoing health and social problems such as illegal substance use (cocaine or marijuana), the results of prevalence-based and incidence-based estimates are often similar. For health problems declining in magnitude, prevalence- based estimates will generally be lower than incidence-based estimates. For emerging health issues such as epidemics of Hepatitis infection, incidence-based estimates generally provide higher estimates than prevalence-based estimates, because many infected persons may still be in the latency phase of the diseases.

Tarricone (2004, 2006) summarizes the situations where which approach is more applicable and useful. The prevalence-based approach can be particularly useful when the main study purpose is:[22,23]

1. To draw an attention from the health policy planners or decision-makers for conditions whose burden has been somehow underestimated. Because of the numerical differences between the prevalence and the incidence approaches, the first serves this purpose better than the incidence based approach.

2. To design cost containment policies. This is because the study provides decision makers with a picture of the global burden and, more importantly, of the major cost components, that is the areas where cost containment policies would have the greatest impact.

The incidence-based approach is particularly useful when the study mainly aims at:[22,23]

1. Considering preventive measures, where the incidence-based approaches therefore provide an estimate of the savings that potentially accrue if the preventive measure is implemented.

2. Analyzing the illness management during the entire period. Through this approach researchers can develop the clinical and therapeutic guidelines designed to increase the effectiveness and the efficiency of whole and each step of disease management.

Prospective vs. retrospective approaches

The COI studies can be performed either in prospective or retrospective way depending on the relationship between the study kick-off and the data collection. In a retrospective approach, all the relevant events have already happened when the study starts, in which we just collect the data that are previously recorded. Conversely, in a prospective approach the relevant events have not already occurred at the beginning of the study, which means that the data collection needs to be done by following-up the patients over time. The prevalence- and incidence-based COI studies can be both performed either in prospective or retrospective way.[23]

The major advantage of retrospective approach is that they are less costly and time consuming than its counterpart because all relevant events have already occurred so that they can be measured and recorded in a dataset. Being efficient in investigating a disease with a long duration, the retrospective method can only be possible with sufficient observational datasets. In prospective approach, however, analysts should be able to design data collection systems they want to adopt. Complete dataset on the illness and the consumption of health care resources at every action and intervention can be made by the analysts from the questionnaires designed and provided to patients, family members and/or health care providers. In studying a disease with relatively long time span, a prospective and incidence-based approach would be considerably expensive and time consuming, where retrospective COI studies may be more efficient in measuring the burden of illness.[23]

Top-down vs. bottom-up vs. econometric approaches

1) Top-down approach

The top-down approach, known as the epidemiological or attributable risk approach, measures the proportion of a disease that is due to exposure to the disease or the risk factors.[24,25] Developed by Morganstern et al. (1980), this approach uses aggregated data along with a population-attributable fraction (PAF) known as epidemiological measure to calculate the attributable costs.[26-28,29] In here, the proportion of medical care for disease B attributable to disease A is measured as follows:

$$PAF = \frac{p_A(rr_{BA} - 1)}{[p_A(rr_{BA} - 1) + 1]}$$

where P_A is the prevalence rate of disease A and rr_{BA} is the unadjusted relative risk of disease B for people with disease A, compared with those without disease A.[26,27,30] However, this equation applies only in limited cases where the condition that other factors

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do not affect the association between the two diseases holds. In general, confounding variables such as age, sex, and other similar factors may be related to both diseases in question. 'Confounding' is known as a distortion or inaccuracy in the estimation of association that occurs when the primary exposure of our interest is mixed up with some other factors associated with the outcome. If a researcher is contemplating to figure out and ascertain the possible causality between physical inactivity and heart disease, age can be a confounding factor because it is associated with the exposure (implying that older people are more likely to be physically inactive), and it is also associated with the outcome because it has been clinically proved that older people are at a greater risk of developing heart disease. If not controlled for, the confounding variables can cause an upward bias (in rare cases, downward bias can occur) in the relative risk and then consequently the value of PAF. The confounding is understood as an existence of distortion in the association between an exposure and an outcome that occurs when the study groups differ with respect to other factors that influence the outcome. Unlike selection and information bias, which can be introduced by the investigator or by the subjects, confounding is a type of bias that can be adjusted and controlled for in the analysis, provided that the investigators have information on the status of study subjects with respect to potential confounding factors.

Similar to confounding explained above, the 'effect measure modification' also known as 'statistical interaction' happens when an unknown 'omitted third variable,' depending upon its level, affects the association between the two diseases through an interaction. It occurs when the magnitude of the effect of the primary exposure on an outcome differs depending on the level of a third variable.[31,32] In this situation, computing an overall estimate of association or causality sometimes leads to misinterpretation. A good way to identify effect measure modification is to examine the association separately for each level of the third variable. If a clinical trial is carried out and the drug is shown to statistically significantly reduce total cholesterol level and at the same time with a data scrutiny, the researchers found out that the drug is only efficacious in patients with a specific genetic biomarker and no effects on patients without it. In here, the drug effectiveness varies among the patients with or without the marker.

2) Bottom-up approach

In a bottom-up approach, the cost estimation can be stratified into two steps. The first step is to measure and quantify the health inputs employed and the second step is to estimate the unit costs of the inputs used to produce and confer specific medical and health care services. The total costs come out through the multiplication of unit costs by the quantities used. The major difficulty arises here since the data needed and available will vary with the scope of the study. In most cases, national level survey datasets are mainly used because they provide reliable data on medical care utilization so that researchers are relatively easily able to quantify the amount of medical care services along with unit costs or price values.

The comprehensive studies can often be advantageous in allocating total national expenditures among the major diagnostic categories, then we can avoid the risk that the sum of treatment costs of individual diseases is greater than national health expenditure (NHE) in a given country.[16] But the top-down approach is likely to present misallocation of costs because using the NHE may lead to either under- or over-estimation of total direct costs. Besides, the exclusion of cost categories in NHE accounting such as transportation and informal care also biases the estimates of costs by disease category since different disease categories may absorb different non-health costs. And, another problem with this method is that all costs are attributed only to the primary diagnosis, which may cause a serious problem if we consider that a relevant part of all hospital discharges involve patients with multiple diagnoses.[23]

3) Econometric approach

The econometric approach tries to estimate the difference in costs between a cohort with the disease and another cohort without the disease. The two cohorts are matched, usually through a series of regression analyses, by various demographic and mediating factors and other chronic conditions. Within the econometric approach, there are two major methods of estimating costs: a mean differences approach and a multiple-stage regression approach. The mean differences approach compares the mean costs incurred by each of the two cohorts to determine the incremental difference attributable to the disease.[33,34] Studies using the mean differences approach sometimes only provide the per case cost of the disease rather than total cost.

A multiple-stage regression method is typically performed if there are a large number of cases with zero costs and a few cases of very high costs. The incremental cost of the disease is measured through a comparison of the coefficients from the regression analyses with the disease dummy variable included to the regression estimate with the disease dummy variable excluded. The regression analysis often uses a two-stage method to estimate COI, al-

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though there are many other possible variants for each of the regression analysis depending upon the types of the dataset and the research purposes.[35-38] Because the econometric approach measures the incremental difference between persons who have the disease and those who do not, it often only requires one dataset, which is understood as a strength in adopting this approach.[33,37] While the top-down approach usually requires cost data as well as on the relative risks which are needed to calculate the PAFs, the bottom-up approach often requires data from multiple sources for the unit cost and utilization rate of the different types of health care. Though each method is valid and appropriate in some situations, in most cases the econometric approach has more advantage in requiring less data.

PERSPECTIVES OF COI STUDIES

The COI studies may be carried out from a variety of perspectives, each of which then includes slightly different cost items to eventually lead to different and wide range of results for the same illness. These perspectives may measure costs to a society, health care system, third-party payers, business sectors, the government, and the participants and their families.[39-41] However, each perspective provides useful information about the costs to the particular group. Table 2 presents the cost categories included in each perspective.

In general, the broader societal perspective is preferred, because the impact of a condition is not solely on the individuals or organizations that are directly involved. Through the societal perspective, we can detect 'cost shifting' between sectors and account for alternative resources used outside the health care sector.[42,43] The societal perspective is the most comprehensive because it includes all direct medical costs and indirect costs for all members in a given society where they are involved, and it is often preferred because it allows a complete analysis of all of the opportunity costs attributable to a disease and is recommended for possible cost analyses such as CBA, CEA, and CUA.[3] But it is theoretically appropriate that this perspective does not include payment or income transfers such as medical aid benefits paid to individuals because they represent just a shift in resources not a use of them, meaning that the money just changes hands not explicitly creating any additional benefit or effectiveness at social level. This perspective, however, requires presumably the biggest sizable data, often making it difficult to use in specific cases with less prevalent diseases. This is especially true with less common diseases or orphan diseases, where data are more limited with few cases. In these situations, data from a third-party payer would be reliable (such as National Health Insurance Statistical Yearbook, Korean Health Panel Survey, etc.), in which the societal approach is clearly not feasible. Because of the relatively larger scope and range of costs, the societal and health care system perspectives inevitably tend to result in higher cost estimates than any other approaches. The business perspective tends to utilize its inside information on expenses in estimating the COI, where frequently the friction cost method is dominant. This perspective is highly likely to underestimate the disease burden especially when the business is designed to pursue its maximized profit or minimized production costs.

Table 2. Costs included in cost-of-illness studies by perspective

Perspective	Medical costs	Morbidity costs	Mortality costs	Transportation/ Nonmedical costs	Transfer payments
Societal	All costs	All costs	All costs	All costs	-
Health care system	All costs	-	-	-	-
Third-party payer	Covered costs	-	Covered costs	-	-
Business	Covered costs (self-insured)	Productivity losses (absenteeism)	Productivity losses	-	-
Government	Covered (Medical aid)	-	-	Criminal justice costs	Attributable to illness
Participants and families	Out-of-pocket costs	Wage losses/ Household production	Wage losses/ Household production	Out-of-pocket costs	Amount received

Source: Luce et al. 1996.37.[40]
COI, cost of illness.

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PRESENT VALUE WITH DISCOUNTING AND SENSITIVITY ANALYSIS

Discounting is an economic method that captures an individual's preference for income or payment today rather than that in the future. This time preference is often explained by the opportunity cost of interest, but it varies with individuals' attitudes toward future (i.e., far-sighted or more rational vs. myopic or less rational) so that its value can also be endogenously determined. Income earned now can bear interest through investment so people want to get partially or fully compensated when they rather choose to have money later to feel indifferent between these two portfolio options, having money now or having more money later. For example, given a 3 percent of annual interest rate, a payment of $500 today is worth more than the same payment in one year because $15 of interest will be generated if the payment is received today and invested as an interest-bearing security at that interest rate for one year. Discounting allows us to calculate the present value (PV) of income or payments that occur in the future. The PV of a specific amount received in the future after n-year of maturity when the discount rate (which is closely related to the real interest rate) is r is given by the formula of

$$PV = \frac{payment}{(1+r)^n}$$

Discounting is relevant for direct and indirect costs that accrue past the first year. A number of discount rate values can be adopted to discount the future monetary amounts, with each representing a slightly different approach. The discount rates range from zero percent to 10 percent. In US, mainly 3 percent of discount rate is suggested in conducting CEA, while in Korea 5.5 percent is mostly applied as a social discount rate in most of the feasibility studies and the policy evaluations conducted by most of the government agencies and research institutes.[3] Other discount rates can be applied to determine their effect on the cost estimates and the possible range of movements of cost estimates in terms of sensitivity analysis.[11,17,18] Sensitivity analysis is understood as a technique used to determine how different values of an explanatory variable will have an effect on a particular explained variable under the given conditions and assumptions. By creating a set of scenarios, the investigators can determine how changes in one variable will impact the target variable and realize which parameters are the key drivers of a model's results.

There are two types of sensitivity analysis; one-way sensitivity analysis and probabilistic sensitivity analysis. The former, normally by varying the parameters according to the confidence intervals of the data, allows researchers and reviewers to assess the impact that changes in a certain parameter will have on the model's results, while the latter is understood as a useful technique in quantifying the level of confidence that a decision-maker has in the conclusions of an economic evaluation and COI studies. The results of one-way sensitivity analysis can be shown graphically in the form of a tornado diagram. In probabilistic sensitivity analysis, instead of assigning a single value to each parameter, computer software such as TreeAge, WinBUGS, Crystal Ball will be used to assign a distribution to all parameters in the model based upon the average, the standard deviation, and the shape of the distribution of each parameter. The results of probabilistic sensitivity analysis are typically shown using an incremental cost-effectiveness plane, where each iteration result from software running is plotted on a chart.

CONCLUSION

The COI studies are considered to be an important and essential measurement technique in health and medical sciences. By measuring and comparing the economic BOD to society, health care decision makers can benefit in setting up and prioritizing health care policies and interventions that they are supposed to implement. Using economic theories, this paper introduces a variety of study methods in estimating the COI associated with mortality, morbidity, and disability, etc. It also presents the concepts and scopes of costs along with different cost categories from different research perspectives in cost estimations. And by discussing the epidemiological and economic grounds of COI studies, it aims to further achieve the knowledge on several evaluation techniques at more advanced level such as CBA, CEA, and CUA. The COI studies are a descriptive study that can provide information to support the political process as well as the management functions of a various levels of health care providers and organization. To successfully carry out the COI studies, the study should be designed in an innovative way so that it can eventually identify the different subjects who bear the costs and explain the possibility that the results of COI can vary across different study designs. Observational studies, whatever methods discussed above are chosen, the cost evaluation based upon the objective accounting rules and principles can meet these goals.

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Conflicts of Interest

The author has no conflicts to disclose.

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