COST-OF-ILLNESS STUDIES IN CHRONIC CONDITIONS

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Declaration

I hereby declare that this thesis is my original work and it has been written by me in its entirety. I have duly acknowledged all the sources of information which have been used in the thesis.

This thesis has also not been submitted for any degree in any university previously.

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Summary

Chronic diseases have been recognised as a major health issue, and their chronic nature along with their complications result in a significant economic burden. Because of the increasing prevalence of these diseases, a better understanding of the cost-of-illness (COI) related to them is important. In Singapore, little is known about the costs of chronic conditions and their associated factors. In this thesis study, the costs of three common chronic conditions were estimated: (i) diabetes mellitus (DM), (ii) strokes and (iii) osteoporotic fractures.

First, a systematic review was conducted of MEDLINE and Scopus journal articles published in English from 2007 to 2011 that reported the cost of type 1 and/or 2 DM. The systematic search yielded 30 articles, which varied considerably in their study design, perspective and included cost categories. It was found that inpatient costs was the major contributor to direct cost in half of the studies that include inpatient costs, physician services and medications.

Second, direct medical costs associated with type 2 diabetes mellitus (T2DM) was estimated and the relationship between both demographic and clinical state variables and the total estimated expenditure were examined. Of the total healthcare expenditure, the main cost driver was inpatient costs. Accident and emergency (A&E) services were only a small proportion of the total costs, while the major source of cost for

outpatient services was physician visits. DM interventions such as the use of insulin only and the combination of both oral medications and insulin as well as having cerebrovascular, cardiovascular, peripheral vascular disease and nephropathy complications were found to be independent determinants of total costs.

Third, the direct medical cost associated with stroke was estimated, and the relationship between the total calculated costs and individual demographic characteristics, type of stroke, length of post-stroke period, complications and comorbidities were examined. Inpatient costs accounted for the majority of the total estimated healthcare expenditure, followed by outpatient services and A&E services. Healthcare expenditure across all services was substantially higher in acute patients than prevalent patients. Independent determinants of greater total costs were stroke types such as ischaemic stroke (IS), subarachnoid haemorrhage (SAH) and intracerebral haemorrhage (ICH), shorter post-stroke period, having more than one complication and a greater number of comorbidities.

Fourth, a prospective study was conducted to estimate the total direct and indirect costs of osteoporotic fractures in Singapore. Taking both the hospital's and patient's perspective, the main cost contributor in the direct medical cost was inpatient costs, while the major source of cost for outpatient services was rehabilitation services. Informal care accounted for the majority of the total estimated expenditure for indirect

costs, and this amount was substantially higher in patients with acute fracture. Overall, direct costs were significantly higher than indirect costs for both acute and prevalent patients.

In conclusion, this thesis provided important information on the economic burden of major chronic conditions in Singapore's population. The findings of this project have paved the way for future pharmacoeconomic evaluations, which are expected to contribute to the development of healthcare policies, appropriate health resource allocation and justification of intervention programs.

List of Tables

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List of Abbreviations, Acronyms and Symbols

β-coefficient	-	beta coefficient
€	-	Euro
£	-	Pound
95% CI	-	95% confidence interval
A&E	-	accident and emergency
AU	-	Australian dollar
bil	-	billion
BMD	-	bone mineral density
BMI	-	body mass index
CAD	-	Canadian dollar
CDMP	-	Chronic Disease Management Programme
CDMS	-	Chronic Disease Management System
CNY	-	Chinese Yuan
COI	-	cost-of-illness
COPD	-	chronic obstructive pulmonary disease
CS	-	cross-sectional
DALYs	-	disability-adjusted life-years
DM	-	diabetes mellitus
HbA1c	-	glycated haemoglobin
IB	-	incidence-based
ICD	-	International Classification of Diseases

ICD-9-CM	-	International Classification of Diseases Ninth Revision
ICH	-	intracerebral haemorrhage
INR	-	Indian Rupee
INT	-	international dollar
IS	-	ischaemic stroke
KRW	-	Korean Won
LDL-c	-	low-density lipoprotein cholesterol
LOS	-	length of stay
M	-	matched
MeSH	-	Medical Subject Headings
mil	-	million
MM	-	Markov modeling
MOH	-	Ministry of Health
MOM	-	Ministry of Manpower
MRI	-	magnetic resonance imaging
MRT	-	Mass Rapid Transit
MVC	-	macrovascular complications
NA	-	not applicable/not available
NHG	-	National Healthcare Group
NM	-	non-matched
NR	-	not reported
NT	-	New Taiwan dollar
NUH	-	National University Hospital

P	-	prospective
PB	-	prevalence-based
Ph.D.	-	Doctor of Philosophy
pppy	-	per patient per year
pt	-	patient
QALYs	-	quality-adjusted life years
R	-	retrospective
S	-	Singapore dollar
SAH	-	subarachnoid haemorrhage
SD	-	standard deviation
SOC	-	specialist outpatient clinic
SPSS	-	Statistical Package for the Social Sciences
SUS	-	Brazilian Public Health System
T1	-	type 1
T2	-	type 2
T2DM	-	type 2 diabetes mellitus
TCM	-	traditional Chinese medicine
TIA	-	transient ischaemic attack
UACR	-	urine albumin-to-creatinine ratio
US	-	US dollar
U.S.	-	United States
USA	-	United States of America
UTI	-	urinary tract infection

WHO	-	World Health Organisation
X-ray	-	electromagnetic radiation
yr	-	year

Publications

Peer-Reviewed Papers

- **Ng CS**, Lee JYC, Toh MPHS, Ko Y. Cost-of-Illness Studies of Diabetes Mellitus: A Systematic Review. *Diabetes Res Clin Pract.* 2014;105:151-63.

- **Ng CS**, Toh MPHS, Ko Y, Lee JYC. Direct Medical Cost of Type 2 Diabetes in Singapore. *PLoS ONE.* 2015; 10(3): e0122795.

Podium Presentation

- **Ng CS**, Lee JYC, Toh MPHS, Ko Y. Cost-of-Illness Studies of Diabetes Mellitus: A Systematic Review. Healthcare Decision Making in the Age of Personalised Medicines Symposium, May 18-19, 2012, Singapore.

Poster Presentation

- **Ng CS**, Lee JYC, Toh MPHS, Ko Y. Cost-of-Illness Studies of Diabetes Mellitus: A Systematic Review. ISPOR 18th Annual International Meeting, May 18-22, 2013, New Orleans, LA, USA.

- Ng JY, **Ng CS**, Toh MP, Ko N. Estimating the Cost of Stroke in Singapore. Annual Pharmacy Research Awareness Symposium, April 9, 2014, Singapore.

- Fong SY, Lau TC, **Ng CS**, Ko N. Validation of the mini-Osteoporosis Quality of Life Questionnaire in Singapore. Annual Pharmacy Research Awareness Symposium, April 9, 2014, Singapore.

Featured Study on Faculty of Science Website

- **Ng CS**, Lee JYC, Toh MPHS, Ko Y. Cost-of-Illness Studies of Diabetes Mellitus: A Systematic Review, 2014 [cited 2014 October 20]; Available from: http://www.science.nus.edu.sg/research-highlights/1062-medical-cost-for-diabetes

CHAPTER ONE

Introduction

Chapter 1 Introduction

1.1 Cost-of-Illness Studies – Determining the Total Financial Burden of a Disease

1.1.1 Overview

Cost-of-illness studies summarise the resources used and lost as a result of a particular disease, making possible an analysis of the medical and economic burden that a disease may have on society as a whole, the health service and/or the patient [1-3]. It should be noted that COI studies serve a different purpose than health economic evaluations such as cost benefit analysis, cost effectiveness analysis, or cost utility analysis, which focus on the assessment of the cost of interventions rather than estimating the cost of a particular disease [2].

The framework for present COI studies stems from the work of Fein [4], Mushkin and Collings [5], Weibrod [6], Rice and Cooper [7] and others during the 1950's and 1960's. In particular, in 1966, Dorothy Rice published a monograph that proposed a method of estimating costs from available information in existing data sets. This monograph established what has now become the standard for all COI studies: addressing the economic COI in the two categories of direct costs and indirect costs. The term 'cost' in health economics refers to the value of the outcome of using a particular good or service, rather than its price.

A third category, the psychosocial cost of illness or its impact on quality of life, is often mentioned in the literature but seldom measured in COI studies due to the complexity of such cost measurement [8-12]. COI studies can estimate the maximum amount that could potentially be saved or gained if a disease were to be eradicated [13]. However, arriving at this figure, or even estimating the economic burden of a disease, is a challenging task due to the fact that important data are not always available.

1.1.2 Significance of COI Studies

COI studies translate the burden of a disease into fiscal monetary value. With both direct and indirect costs considered at a micro- and macroeconomic level, this information is used to: (1) quantify the magnitude of the disease in dollar terms; (2) justify intervention programs; (3) develop policies and initiatives to allocate resources appropriately; (4) assist in the allocation of research monies on specific diseases and (5) provide an economic framework for program valuation [14]. Cost estimates provide valuable information to policy makers, healthcare providers, third-party payers, patients and others interested in understanding how their healthcare dollars are being spent [15]. Knowledge of the costs of an illness can help policy makers decide which diseases need to be addressed first by healthcare and prevention policies. Additionally, these studies can indicate for which diseases cures would be especially valuable in reducing the burden of

disease. For specific stakeholders, such as the government, COI studies can show the financial impact a disease has on public programs such as government subsidies or programs [13]. For employers, these studies can show which diseases have a particularly large effect on their costs [16, 17]. Moreover, COI studies provide a framework for the costs estimation in cost-effectiveness and cost-benefit analyses [14, 18]. Therefore, COI studies are a valuable tool for advocating that attention and resources be directed towards a specific disease.

1.1.3 Types of Costs

In a COI, three cost components that can be estimated are: (1) direct (medical and non-medical) costs; (2) indirect costs; and (3) intangible costs. These components are presented in Figure 1.1 as a conceptual framework of the economic burden of diabetes. This framework was an adaptation of a broader framework developed by Kirigia *et al* [19].

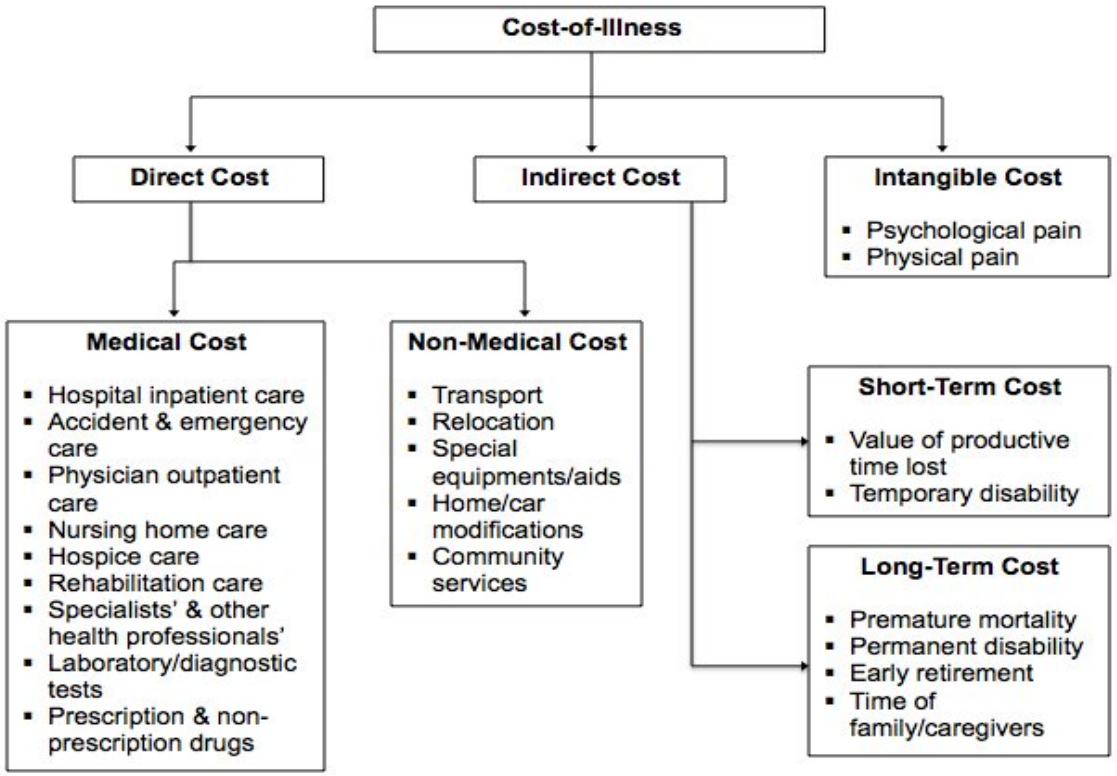

Figure 1.1: Conceptual framework of the economic burden of disease

1.1.3.1 Direct Costs

The direct cost of a disease is derived from the opportunity cost used for the treatment of the disease. Opportunity cost, in the context of COI studies, is the value of all the resources that could have been otherwise allocated but were instead used or lost due to a disease [11]. The fiscal resources that make up the opportunity cost are either direct medical costs or direct non-medical costs.

Direct medical costs are the easiest to calculate and may include costs from hospital inpatient care, physician inpatient care, physician outpatient care, emergency department visits, nursing home care, hospice care, rehabilitation care, specialists' and other health professionals' care, diagnostic tests, prescription drugs and drug sundries, as well as other medical supplies, all of which tend to have receipts of transactions maintained by hospitals, third-party payers, and/or patients [11, 13].

Direct non-medical costs are defined as expenses paid by the patient and his or her family that are directly associated with a disease, but are not medical in nature, for example, transportation, relocation expenses and informal care. Due to their indirect nature, such expenses are easily overlooked but they are a crucial contributor to direct cost estimates [13, 20, 21].

1.1.3.2 Indirect Costs

Indirect costs tend to account for a large proportion of the total estimated cost in COI studies, although several issues exist in the estimation of indirect costs. Indirect costs may incorporate productivity losses due to a disease's morbidity and mortality. Such productivity losses may be of a labour or non-labour nature and, in a manner similar to direct costs, such values represent an opportunity cost. Other indirect costs that may be considered are related to employment costs [13, 21]. Absenteeism is a traditional representation of the loss of productivity that occurs when the workforce population is unable to work as a direct or indirect result of a disease. Typically, work absences reflect a forgone productivity. Meanwhile, decreased productivity due to presenteeism is becoming a recognised measurement of employment cost. Presenteeism contributes to indirect costs because even though a member of the workforce may be present at work, their performance and overall productivity may be negatively affected as a result of the disease [22]. Therefore, indirect cost can account for a substantial proportion of total costs in COI studies.

1.1.3.3 Intangible Costs

Intangible costs typically take the form of quality of life measures, which may include a patient's psychological pain, discomfort, anxiety and distress associated with a disease [23]. As these costs are difficult

to quantify in monetary terms, intangible costs are often excluded from the estimation in COI studies [21].

1.1.4 Perspective

In addition to different types of costs, another important consideration in COI studies is the perspective taken. Depending on the perspective chosen, an estimation of costs will vary. For example, an end-user, such as the patient, may only consider their out-of-pocket costs, whereas an employer may only consider loss of productivity and worker's compensation insurance premiums and/or pay-outs. While both are valid perspectives, they are also narrow and underestimate the total economic burden of a disease, which includes direct, indirect and intangible costs. The most comprehensive way for calculating total costs in COI studies is by taking on a societal perspective [13, 20]. Quantifying COI estimates financed by specific payers provides an additional level of detail that can be used to identify the distribution of resource utilisation and costs across healthcare sectors (i.e. private vs public expenditures) and populations (i.e. gender and age-specific costs) and can assist in an analysis of whether healthcare resources are being equitably distributed [15].

1.1.5 Discounting

Discounting is an economic technique that is based on time preference. It is often explained as an opportunity cost of interest. Discounting calculates the present value of inputs and benefits that will accrue in the future. For example, any income earned today may produce interest through investment.

With regards to COI studies, discounting is only applicable for direct costs and indirect costs that accrue over multiple years. In the literature, discounting figures ranging from 0 to 10 percent have been used. However, in most COI studies, a rate of 3 percent is often selected [13].

1.1.6 Approaches for Cost Estimation

1.1.6.1 Incidence-Based, Prevalence-Based and Present Cost Method

There are three common methods of determining COI estimates. An incidence-based approach examines costs from a cohort of patients, usually from diagnosis until death (lifetime costs) [3, 24]. Incidence-based methods are labour-intensive and require knowledge of the disease course, survival rates, and the impact of the disease on lifetime income. Such an approach is most applicable when making decisions between alternative treatments and studying short-term cost-effectiveness and acute diseases.

A prevalence-based approach differs in that, instead of a lifetime, the cost of a disease is examined in a specific time frame. It is the most commonly used method of estimating the total COI. A prevalence-based method yields findings that can be directly correlated to fiscal impact, cost control and chronic diseases analysis [25].

The third approach is the present cost method. It shares similarities with the prevalence-based approach, but it is unique in that it looks retrospectively in order to estimate losses in productivity. In essence, this method considers mortality losses attributed to individuals who would otherwise have had been alive during a specific time frame. Therefore the opportunity cost is reflected in deaths associated with a particular disease [26].

1.1.6.2 Approach for Direct Costs Estimation

There are two primary approaches to estimating direct costs: the top-down approach and the bottom-up approach. The top-down approach examines costs in an aggregate form for specific diseases. It estimates economic costs by using aggregate data on mortality, morbidity, hospital admissions, general physician visits, disease-related costs and other health-related indicators, which can be identified by primary and/or secondary International Classification of Disease (ICD) codes [27, 28]. For example, in order to derive the cost estimate of medications for the average patient with DM, annual hospital

expenditure on DM-related medications are divided by the number of patients with DM [29, 30].

In the bottom-up approach, also known as micro-costing, it starts with the consumption of resources at the patient's level, using costs of individual units of services performed. For example, in order to derive the cost estimate of medications for individual patients, the number of medications prescribed will be multiplied by unit prices [28, 30].

In recent years, several COI studies have used estimates from the literature to project direct cost. In this approach, previous estimates are adjusted to account for changes over time in prevalence, healthcare use and mortality related to the disease, as well as inflation.

1.1.6.3 Approach for Indirect Costs Estimation

Indirect costs may be derived in three ways: the human capital approach, the friction cost approach, and the willingness-to-pay approach. The human capital approach is the most commonly used method. It considers the foregone income of the patient and their caregivers and takes into account premature mortality or permanent disability, which often includes the value of household work [13, 20]. On the other hand, the friction cost method measures only the production losses during the time it takes to replace a worker [31, 32]. Lastly the willingness-to-pay approach uses various methods such as

surveys or questionnaires to determine the amount an individual would pay to reduce the probability of illness or mortality [13].

1.2 Chronic Conditions – A Major Cause of Mortality and Economic Burden

Chronic diseases are long-lasting medical conditions that are generally progressive. In short, they can be controlled but not cured. They are also the major cause of premature adult deaths in many parts of the world, representing 63.0% of all annual deaths, with most occurring in low- and middle-income countries [33]. According to the World Health Organization (WHO), almost half of all chronic disease deaths occur in people under the age of 70 [33]. The prevalence of chronic conditions continues to increase, and by 2020, an estimated 157 million Americans (nearly 50.0% of the population) are projected to have at least one chronic condition [34].

The three chronic conditions studied in this project are DM, stroke, and osteoporosis-related fractures. Globally, the total number of people with DM is projected to rise from 171 million in 2000 to 366 million in 2030 [35]. Furthermore, approximately 16 million first-occurrence strokes occur around the world per year, accounting for 5.7 million deaths [36]. In 2002, stroke-related disability was judged to be the sixth most common cause of reduced disability-adjusted life-years (DALYs) [37]. As for the third condition studied, in 2000, 9 million osteoporosis-

related fractures occurred worldwide, including 1.6 million hip fractures, 1.7 million forearm fractures and 1.4 million clinical vertebral fractures [38, 39]. Therefore, it is not surprising that considerable attention has been directed toward designing treatment protocols to prevent or inhibit the progression of these three specific chronic conditions.

In Singapore, the prevalence of DM has risen to 12.3% in 2013, from 8.2% in 2004 and 9.0% in 1998 [40, 41]. Furthermore, stroke is the fourth leading cause of death in Singapore, accounting for 9.0% of total deaths, with a prevalence of 3.7% and an incidence of 1.8/1,000 person-years [42, 43]. Also significant are osteoporosis-related hip fractures, with incidence rates that have risen 1.5-fold for men and 5-fold for women since the 1960s. The age-adjusted hip fractures rates among women over the age of 50 years are about 402/100,000 females. Moreover, in 2006, the government introduced the Chronic Disease Management Programme (CDMP) with the aim of providing financial assistance (Medisave) for patients with DM, hypertension, hyperlipidaemia and stroke. It was later expanded to include asthma and chronic obstructive pulmonary disease (COPD), and by 2014, schizophrenia, bipolar disorder, dementia, osteoarthritis, benign prostatic hyperplasia, anxiety, Parkinson's disease and nephrosis/nephritis were also added to the list, giving a total of 15 chronic diseases under the CDMP [44]. This cumulative list serves as a reminder of the growing epidemic currently faced by the Singapore population.

1.3 COI Studies in Patients with DM, Stroke and Osteoporotic Fractures – Top-Ranked Disease Burden with an Increasing Incidence in Asia

The incidence of diabetes, stroke and osteoporosis, three major causes of morbidity and mortality, are increasing rapidly among the Asian population [45-50]. The chronic nature of these conditions along with their complications makes them very costly diseases.

In the United States (U.S.), 84.0% of the total healthcare expenditure in 2006 was for individuals who had one or more chronic conditions [51]. Four of the five most expensive health conditions are chronic conditions [52]. A study conducted in 2007, reported that seven chronic diseases (cancer, diabetes, hypertension, stroke, heart disease, pulmonary conditions, mental illness) have a total impact on the economy of US$1.3 trillion annually. By the year 2023, this number is projected to increase to US$4.2 trillion dollars [53].

The direct costs of DM consume from 2.5% to 15.0% of annual healthcare budgets, depending on local prevalence and available treatments [54]. In 2012, the total estimated cost of diagnosed diabetes in the U.S. was estimated to be US$245.0 billion, including US$176.0 billion in direct medical costs and US$69.0 billion in decreased productivity [55]. Worldwide, stroke consumes about 2–4% of total healthcare expenditure, and in developed countries stroke accounts for

more than 4% of direct healthcare costs [56]. The total annual costs of stroke have been variously estimated at US$40 billion in the U.S. [57], AUS$1.3 billion in Australia [58], and £8.9 billion in the United Kingdom [59]. On the other hand, osteoporosis-related fractures was estimated to be US$20 billion in the U.S. [60], €30 billion in the European Union [61] and AU$1.8 billion in Australia [62].

With an aging population, Singapore is likely to see a marked increase in individuals with complex and chronic diseases, in particular, DM, stroke and osteoporosis.

1.4 Research Significance

In spite of a rising prevalence of chronic conditions in Singapore, the costs of these diseases have not been well examined. Understanding the economic burden of these conditions could enhance better resource allocation and also help develop and improve intervention programs intended to prevent these conditions and complications.

The significance of the first study is to provide a framework for appropriate allocation of healthcare resources and assist government and healthcare practitioners to gain a better understanding of the trends in DM costs. In addition, with the utilisation of the National Healthcare Group (NHG) Chronic Disease Management System (CDMS), the second and third studies' results may be generalized to

the local population. These findings could also serve as an aid for cost management in the treatment of DM and stroke. Finally, the fourth study was one of the few studies that examined both the direct and indirect costs of osteoporotic fractures, which findings may help policymakers and healthcare organisations to assess the impact of interventions on the costs of osteoporosis-related fractures.

1.5 Research Objectives

The main objective of the present thesis is to estimate the total economic burden of DM, stroke and osteoporosis-related fractures in Singapore. This thesis can be broadly separated into two main sections with their specific objectives.

First, the merits of COI studies have been well established in earlier studies [13-15]. Not only are they a valuable tool in establishing the total economic burden of a disease, but they are also an important component for pharmacoeconomic evaluations. However, due to the variability in epidemiologic and economic data availability depending upon the disease in question, making direct comparisons of COI estimates across different populations may be misleading [15]. Therefore, the second chapter aims to:

- Describe the methods used in published DM COI studies.
- Summarise the findings reported in the identified studies regarding the economic impact of DM.

- Identify the strengths and limitations of the various methods utilised.
- Examine how the different methods applied influence reported cost estimates.

Second, Singapore consists of 3 major ethnic groups, namely, the Chinese (74.0%), Malays (13.0%) and Indians (9.1%) [63]. These groups have a high prevalence and incidence of individuals with DM, stroke and osteoporosis-related fractures. In 2005, diabetes was most prevalent among Indians (20.4%), compared to Malays (17.1%) and the Chinese (8.2%) [64]. Chinese and Indian people had similar age-standardised incidence rates of stroke while Malays had the highest from 2009 to 2013 [65]. Age-adjusted hip fracture rates were higher in the Chinese than those in Indians and Malays [47]. Despite the high prevalence and impact of these diseases, their economic impact has not been well studied. Therefore, the third, fourth and fifth chapters aim to:

- Estimate the total direct medical costs associated with T2DM in Singapore and to examine the relationship between demographic and clinical state variables with the total estimated expenditure.
- Estimate the total direct medical costs associated with stroke in Singapore and to examine the relationship between both demographic variables and clinical state variables and the total estimated expenditure.
- Estimate the total direct and indirect costs associated with osteoporotic fractures in Singapore.

CHAPTER TWO

Cost-of-Illness Studies of Diabetes Mellitus: A Systematic Review

Chapter 2 Cost-of-Illness Studies of Diabetes Mellitus: A Systematic Review

Introduction

Diabetes mellitus is a leading cause of mortality worldwide [66], accounting for approximately 4.6 million deaths in 2011 [67]. There are an estimated 382 million people living with DM in 2013 and this number is expected to increase to 592 million by 2035 [68]. This global increase in DM is attributed to population growth and aging and an increasing trend towards unhealthy diets, sedentary lifestyles and obesity [35]. Individuals with DM often develop macrovascular (cardiovascular, cerebrovascular and peripheral vascular diseases) and microvascular (retinopathy, nephropathy and neuropathy) diseases [69, 70]. These chronic complications are highly prevalent in patients with T2DM, with 4 in 10 developing one or more of the complications [71, 72].

The chronic nature of DM and its many complications make it a costly disease [3]. In 2010, the estimated worldwide cost to treat and prevent DM and its associated complications was at least US$376 billion [8]. This led to an increased interest in identifying the costs of DM in order to determine cost-saving solutions for the management of patients with DM. Such aims can be achieved by reviewing studies that examine the cost of DM.

Ettaro et al. performed a systematic analysis of the medical care costs attributable to DM, reviewing approximately 30 published articles worldwide [3]. Nearly a decade later, as attention to the subject increases, we believe an updated review is merited, with Ettaro and colleagues' study providing a useful framework. The present study aimed to review the recently published literature regarding the cost of DM. The objectives are two-fold: (1) to describe the methods used in the identified cost of DM studies and (2) to summarise their study findings regarding the economic impact of DM.

Methods

A systematic review was performed in accordance with a pre-specified protocol. Search results were screened for relevance according to the following inclusion and exclusion criteria.

Inclusion criteria:

1. Original research.
2. English language.
3. Studies that reported COI, healthcare expenditure, or resource utilisation for type 1 and/or 2 DM.

Exclusion criteria:

1. Diabetes management.
2. Gestational diabetes.

3. Economic evaluation of drug or other treatment (e.g. cost-effectiveness analysis).
4. Only projected costs were provided.
5. Only one aspect of costs was provided (e.g. only inpatient costs).
6. No cost data reported.
7. Study population restricted to one hospital or clinic.
8. Conference abstracts, review papers, case reports, letters, comments, or editorials.
9. Animal or in vitro studies.

MEDLINE (via PubMed) and Scopus were the electronic databases searched in February 2012. The medical subject heading (MeSH) terms used for the search were “cost of illness” and “diabetes” and the keyword search terms were “burden of illness”, “cost”, “cost analysis”, “cost of disease”, “cost of illness”, “disease burden”, “economic burden”, “healthcare costs” and “diabetes”. Recently published studies and studies on Scopus were searched using only keywords as the new studies had not been indexed for MeSH and Scopus has no MeSH function. A Google Scholar search was also conducted with similar keyword search terms. In addition, a manual search of the bibliographies of the relevant articles identified was conducted. The search was limited to human studies published in English from January 2007 to December 2011 and confined to those addressing costs among large populations, such as nations or insurance pools.

Screening and data extraction

To evaluate the relevance of the articles retrieved from the literature search, two tiers of screening were performed by two trained reviewers. In the first step, only the articles with the words "costs" and "diabetes" or similar words in the title were included. In the second step, the two reviewers independently read and evaluated the abstract and, if necessary, the full texts of all the articles that passed the first round of screening based on the inclusion and exclusion criteria. In circumstances of uncertainty or discrepancy between the two reviewers, a discussion was held and, if necessary, a third reviewer's opinion was sought until a consensus was reached.

Essential information about the study methods and findings were then extracted from the articles that passed the two-step screening process and are summarised in Tables 2.1-2.3. For studies that presented both current and projected cost estimates, only current estimates were reported. Studies reporting excess costs due to DM and its complications were also reviewed and summarised in Tables 2.4 and 2.5 respectively. As an effort to ascertain the accuracy and completeness of the information retrieved, we emailed a summary information sheet to all the corresponding authors of the studies. The information sheet included all the information extracted from each study (e.g., year of costing, currency used and type of DM) by the investigators of the present review study. The information sheet was

then sent to the corresponding authors of each study to verify the accuracy of the information extracted. The authors were asked to reply with tracked changes if there was any error or misinterpretation. As different currencies were used in the cost estimates, cost values were converted to US dollars using the FX currency converter for comparison [73].

Results

The initial search strategy yielded 5493 studies, from which 1502 duplicates were removed (Figure 2.1). Of the remaining 3991 articles, 429 passed the first level of screening and 400 of those were excluded at the second screening, leaving 29 articles for data extraction. During data extraction, the bibliographies of the 29 articles were searched manually and one additional article that met the selection criteria was found, giving the total of 30 articles included in this review.

Characteristics of COI articles

Table 2.1 summarises the methods and major findings of the 30 articles reviewed. One third of the studies (n = 10) were conducted in the United States (U.S.) [24, 74-82] and the others were conducted in the WHO African region [19], Brazil [83], Canada [84], the Caribbean region [85], China [54], Germany [86, 87], Greece [88], India [89, 90], Iran [91, 92], Japan [93], the Netherlands [94], Norway [95], Sudan [96],

Sweden [97-99] and the United Kingdom [100]. Approximately half of the studies (n = 14) estimated both the overall direct and indirect costs of DM, with two studies also providing an estimate of lifetime costs [24, 81]. Direct costs were included in all but one study where only incremental cost was reported. Indirect costs were reported in thirteen studies and intangible costs were estimated in only one study [90]. Furthermore, eight studies extrapolated the cost estimates to the national population.

Amongst the reviewed studies, the societal perspective was the most commonly taken (n = 11), followed by the healthcare system (n = 7) and third-party payer perspective (n = 7). Most authors did not explicitly state the perspective taken. More than half of the reviewed studies included both type 1 and 2 DM patients (n = 17). The human capital approach was used in a majority of the studies (n = 10) that included indirect cost estimates. Moreover, most employed a retrospective (n = 18) and prevalence-based (n = 28) study design, while two [24, 80] adapted a Markov model to estimate costs.

Healthcare cost components

The healthcare components considered in the direct and indirect cost estimates varied among the studies (Tables 2.2 and 2.3). For direct cost estimation, most studies included costs associated with hospital inpatient care, physician services and drugs. In those studies that

reported indirect cost estimates, all but two included costs associated with absenteeism and more than half took into account disability and premature mortality. Only three studies considered the foregone earnings as a result of DM-related presenteeism.

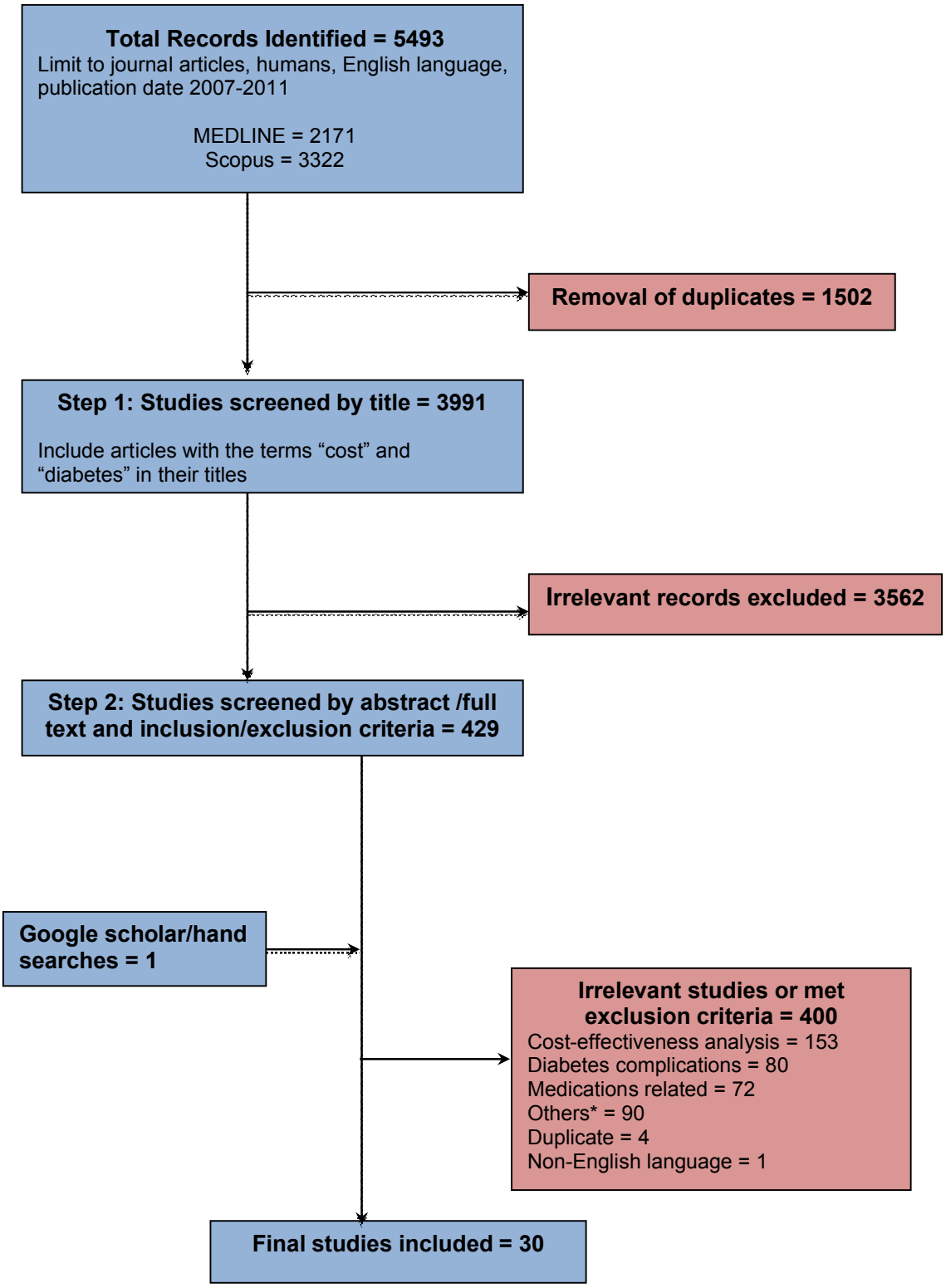

Figure 2.1: Flowchart of the number of articles retrieved from literature search and selection process
*Includes articles that did not fall into the above exclusion categories.

Table 2.1: Characteristics of cost-of-illness studies for diabetes mellitus, arranged by alphabetical order & reflecting costs incurred in the year stated

	Study (year of costing)	DM type	Data source	Sample size	Study design	Study perspective	Total costs*	Direct costs*	%	Indirect costs*	%
Abdulkadri et al. [85] (2001)	Caribbean region (4 countries included)	1 & 2	Ministry of Health data	360,002	R/PB	Societal	US$753mil (US$624.9mil)	US$263.9mil	42.2	US$357.6mil	57.2
American Diabetes Association [74] (2007)	United States	1 & 2	Multiple data sources	17,486	R/PB	Healthcare system	US$174bil	US$116bil	66.7	US$58bil	33.3
Athanasakis et al. [88] (2007)	Greece	2	Medical records	102	R/PB	Third-party payer	€1bil[b] (US$1.3bil)	€1,297.3/pt (US$1,725.5/pt)			
Bahia et al. [83] (2007)	Brazil (8 cities included)	2	Patient survey & medical records	1,000	CS/PB	Brazilian Public Health System (SUS) & societal	US$2,108/pt	US$1,335/pt	63.3	US$773/pt	36.7
Balu [75] (2004)	United States	1 & 2	National survey	13,922,448	R/PB	Societal		US$82.2bil[b] (incremental direct costs comparing DM & no DM)			
Bogner et al. [76] (2000 & 2001)	United States	1 & 2	Insurance claims	971	R/PB	Healthcare system		US$10,566/pt			
Bolin et al. [97] (1987 & 2005)	Sweden	1 & 2	Multiple data sources	150,000 (1987); 254,000 (2005)	R/PB	Healthcare system	€439mil (US$583.9mil) (1987); €920mil (US$1.2bil) (2005)	€196mil (US$260.7mil) (1987); €337mil (US$443mil) (2005)	44.6 (1987); 37.0 (2005)	€243mil (US$323.2mil) (1987); €583mil (US$766.4mil) (2005)	55.4 (1987); 63.9 (2005)

Table 2.1: Characteristics of cost-of-illness studies for diabetes mellitus, arranged by alphabetical order & reflecting costs incurred in the year stated

	Study (year of costing)	DM type	Data source	Sample size	Study design	Study perspective	Total costs*	Direct costs*	%	Indirect costs*	%
Buescher et al. [77] (2007 - 2008)	North Carolina, United States	1 & 2	Insurance claims	127,991	R/PB	Third-party payer		US$4,098/pt or US$524.6mil			
Currie et al. [100] (1997-2007)	United Kingdom	1 & 2	General practitioner database	T1: 11,300; T2: 114,752	R/PB	Healthcare system		T1: £742/pt (US$1,180/pt); T2: £602/pt (US$957.4/pt) (1997); T1: £1,323/pt (US$2,104/pt); T2: £1,080/pt (US$1,717.6/pt) (2007)			
Durden et al. [78] (2000 & 2005)	United States	2	Insurance claims	21,592 (2000); 127,254 (2005)	R/PB	Employer		US$12,423/pt (2000); US$12,733/pt (2005)			
Elrayah-Eliadarous et al. [96] (2005)	Khartoum State, Sudan	2	Patient survey	822	CS/PB	Patient		US$175/pt			
Esteghamati et al. [91] (2004-2005)	Tehran, Iran	1 & 2	Patient survey	710	P & CS patient survey/ PB	Patient	US$191.9/pt[a]; US$141.6mil[a] or US$744.2mil[ab]	US$152.3/pt[a]; US$112.4mil[a] or US$590.7mil[b]	79.4	US$39.6/pt[a]; US$29.2mil[a] or US$153.5mil[b]	20.6
Fu et al. [79] (2004 & 2006)	United States	1 & 2	National survey	4,233	CS/PB	Societal	US$13,130/pt	US$10,845/pt	82.6	US$2,285/pt	17.4
Gonzalez et al. [24] (Multiple years)	Colombia, United States	2	Multiple data sources	NA	P MM/IB	Societal & Ministry of Health	US$847/pt (MOH); US$2.7bil[b] or lifetime costs of US$27,140/pt (societal)	US$288/pt (MOH) or US$921mil[b] (societal)	34	US$559/pt (MOH) or US$1.8bil[b] (societal)	66.0

Table 2.1: Characteristics of cost-of-illness studies for diabetes mellitus, arranged by alphabetical order & reflecting costs incurred in the year stated

	Study (year of costing)	DM type	Data source	Sample size	Study design	Study perspective	Total costs*	Direct costs*	%	Indirect costs*	%
Huang et al. [80] (Multiple years)	United States	2	National survey	NA	MM/IB PB	Healthcare system & societal		US$113bil or US$45bil for Medicare users			
Javanbakht et al. [92] (2009)	Tehran & Fars, Iran	2	Medical records & patient survey	4,500	CS/PB	Societal	US$1,707.4/pt or US$3.8bil[b]	US$842.6/pt or US$2.0bil[b]	49.3	US$864.8/pt or US$1.7bil[b]	50.7
Kirigia et al. [19] (2000)	WHO African region	1 & 2	Multiple data sources	7.02 mil	R/PB	Societal	INT$3,633/pt (US$3,633/pt) or INT$25.5bil (US$25.5bil)	INT$8.1bil (US$8.1bil)	31.8	INT$17.4bil (US$17.4bil)	68.2
Köster et al. [86] (2000-2007)	Germany	1 & 2	Insurance claims	25,482 (2000); 29,379 (2007)	R/PB	Third-party payer		€5,197/pt[a] (US$6,912.5/pt) (2000); €5,726/pt[a] (US$7,616.1/pt) (2007)			
Kumar et al. [89] (2005)	Delhi, India	2	Community survey	819	CS/PB	Patient		US$150/pt			
Martin et al. [87] (1995-2003)	Germany	2	Public health insurance database	3,142	R/IB	Third-party payer		€3,210/pt (US$4,269.6/pt) for the mean observation period of 6.5yrs			
Nakamura et al. [93] (1990-2001)	Shiga, Japan	1 & 2	Insurance claims	138	P/PB	Third-party payer		US$328/pt/month			
Pohar & Johnson [84] (2001)	Saskatchewan, Canada aboriginals	1 & 2	Administrative databases	46,914	R/PB	Healthcare system		CAD$3,622/pt (US$3,625.9/pt)			

Table 2.1: Characteristics of cost-of-illness studies for diabetes mellitus, arranged by alphabetical order & reflecting costs incurred in the year stated

	Study (year of costing)	DM type	Data source	Sample size	Study design	Study perspective	Total costs*	Direct costs*	%	Indirect costs*	%
Ringborg et al. [98] (2004)	Uppsala county, Sweden	2	Multiple data sources	8,230	R/PB	Healthcare system		€3,602/pt (US$4,791/pt)			
Solli et al. [95] (2005)	Norway	1 & 2	National register databases & patient survey	4.6 mil database & 584 survey	R & CS/PB	Societal	€292.5mil (US$389.1mil)	€222.4mil (US$295.8mil)	76	€70.1mil (US$93.2mil)	24.0
Tao et al. [81] (1999-2005)	United States	1	National surveys	1.1 mil	R/IB & PB	Societal	US$17,032/pt; US$14.4bil or lifetime costs of US$422.9bil	US$9,868/pt; US$6.9bil or lifetime costs of US$133.7bil	47.9	US$7,164/pt; US$7.5bil or lifetime costs of US$289.2bil	52.1
Tharkar et al. [90] (2009)	Chennai, India	2	Patient survey	718	CS/PB	Societal	US$628.3/pt or US$31.9bil[b]	INR$25,391/pt (US$525.5/pt)	83.6	INR$4,970/pt (US$102.8/pt)	16.4
Tunceli et al. [82] (2007)	United States	1 & 2	Insurance claims	T1: 12,096; T2: 256,245	R/PB	Third-party payer		T1: US$6,247/pt; T2: US$3,002/pt (by disease-attributable cost estimation method) T1: US$14,060/pt; T2: US$8,070/pt (by matched cohort cost estimation method)			
van der Linden et al. [94] (2000-2004)	Netherlands	1 & 2	National database	454,000 (2000); 641,200 (2004)	R/PB	Third-party payer		€974/pt[ab] (US$1,295.5/pt) or €717.4 mil[ab] (US$954.2mil) (2000); €1,283/pt[ab] (US$1,706.5/pt) or €1.4bil[ab] (US$1.9bil) (2004)			

Table 2.1: Characteristics of cost-of-illness studies for diabetes mellitus, arranged by alphabetical order & reflecting costs incurred in the year stated

	Study (year of costing)	**DM type**	**Data source**	**Sample size**	**Study design**	**Study perspective**	**Total costs***	**Direct costs***		**Indirect costs***	
									%		%
Wang et al. [54] (2007)	China (4 cities included)	2	Patient survey	2,040	CS/PB	Patient	US$1707.8/pt or US$26.0bil[b]	US$1501.7/pt	87.9	US$206.1/pt	12.1
Wiréhn et al. [99] (2005)	Östergötland & County, Sweden	1 & 2	Administrative database	20,876	CS/PB	Government		€4,474/pt[a] (US$5,950.8/pt)			

* Cost converted to US-dollar; costs may not add up to exact amount due to rounding to one decimal place.
[a] Cost figures standardised to match age and gender distribution in the overall population.
[b] Cost figures for the entire country's population.
bil=billion; **CS=**cross-sectional; **DM=**diabetes mellitus; **IB=**incidence-based; **INT=**international dollars; **mil=**million; **MM=**Markov modeling; **NA=**not applicable; **P=**prospective; **PB=**prevalence-based; **pt=**patient; **R=**retrospective; **T1=**type1; **T2=**type 2; **yr=**year.

Table 2.2: Components of direct healthcare costs for diabetes mellitus

Study	Hospital inpatient	Physician services[a]	Emergency outpatient	Drugs	Laboratory tests	Other health professional/ allied health	Nursing home care	Rehabilitation/ hospice care	Vision care	Skin care	Daily self-management	Home healthcare	Transport	Informal care/ caregiver
Abdulkadri et al. [85]	✓	✓		✓	✓									
American Diabetes Association [74]	✓	✓	✓	✓		✓	✓	✓				✓		
Athanasakis et al. [88]		✓		✓	✓	✓								
Bahia et al. [83]		✓	✓	✓	✓	✓							✓	✓
Balu [75]	✓	✓	✓	✓								✓		
Bogner et al. [76]	✓	✓	✓	✓	✓		✓	✓				✓		
Bolin et al. [97]	✓			✓		✓								
Buescher et al. [77]	✓	✓		✓		✓	✓					✓		
Currie et al. [100]		✓		✓										
Durden et al. [78]	✓	✓	✓	✓	✓									

Table 2.2: Components of direct healthcare costs for diabetes mellitus

Study	Hospital inpatient	Physician services[a]	Emergency outpatient	Drugs	Laboratory tests	Other health professional/ allied health	Nursing home care	Rehabilitation/ hospice care	Vision care	Skin care	Daily self-management	Home healthcare	Transport	Informal care/ caregiver
Elrayah-Eliadarous et al. [96]		✓		✓	✓								✓	
Esteghamati et al. [91]	✓	✓	✓	✓	✓				✓	✓	✓		✓	
Fu et al. [79]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Gonzalez et al. [24]	✓	✓		✓	✓	✓								
Huang et al. [80]	✓	✓	✓	✓	✓				✓					
Javanbakht et al. [92]	✓	✓		✓	✓	✓		✓				✓	✓	✓
Kirigia et al. [19]	✓	✓		✓	✓								✓	✓
Köster et al. [86]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	
Kumar et al. [89]		✓	✓	✓	✓						✓			
Martin et al. [87]		✓		✓							✓			
Nakamura et al. [93]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

Table 2.2: Components of direct healthcare costs for diabetes mellitus

Study	Hospital inpatient	Physician services[a]	Emergency outpatient	Drugs	Laboratory tests	Other health professional/ allied health	Nursing home care	Rehabilitation/ hospice care	Vision care	Skin care	Daily self-management	Home healthcare	Transport	Informal care/ caregiver
Pohar & Johnson [84]	✓	✓												
Ringborg et al. [98]	✓	✓		✓							✓			
Solli et al. [95]	✓	✓	✓	✓	✓	✓					✓	✓		
Tao et al. [81]	✓	✓	✓	✓					✓			✓		
Tharkar et al. [90]	✓	✓	✓	✓	✓						✓		✓	✓
Tunceli et al. [82]	✓	✓	✓	✓										
van der Linden et al. [94]	✓			✓										
Wang et al. [54]	✓	✓		✓	✓								✓	✓
Wiréhn et al. [99]	✓	✓	✓	✓	✓	✓					✓			

[a] Includes either inpatient, outpatient or both
NR=not reported

Table 2.3: Components of indirect healthcare costs for diabetes mellitus

Study	Absenteeism	Presenteeism	Permanent disability	Early retirement	Premature Mortality
Abdulkadri et al. [85]	✓		✓		✓
American Diabetes Association [74]	✓	✓	✓		✓
Bahia et al. [83]	✓			✓	
Bolin et al. [97]			✓		✓
Esteghamati et al. [91]	✓				
Fu et al. [79]	✓				
Gonzalez et al. [24]	✓		✓		✓
Javanbakht et al. [92]	✓	✓	✓		✓
Kirigia et al. [19]	✓		✓		✓
Solli et al. [95]	NA	NA	✓		
Tao et al. [81]	✓	✓	✓		✓
Tharkar et al. [90]	✓				
Wang et al. [54]	✓				

NA=not available

Cost of DM

Direct and indirect costs of DM

The costs of DM reported by different studies varied significantly (Table 1). The annual direct costs for the total population in country ranged from an annual total of US$112.4 million in Iran to US$116 billion in the U.S. and from a per patient per year (pppy) of US$150 in India to US$14,060 in the U.S. Notably, there was a substantial difference in cost estimates between the two studies done in India [89, 90]. The direct costs were US$150 pppy for the study conducted in Delhi and US$525.5 pppy for the study conducted in Chennai. Furthermore, eight out of the thirteen studies that included both direct and indirect costs suggested that direct costs were higher than indirect costs. The general consensus from half of the studies (n=10) [54, 74, 76, 78, 81, 86, 90, 95, 98, 99] that included inpatient costs, physician services and medications was that inpatient costs was the major contributor to direct costs.

Excess cost of DM versus non-DM

Diabetes-related excess costs were reported in thirteen studies, with eight that included a matched control group (Table 2.4). The difference between DM patients and non-DM ranged from US$123.1 to US$10,837 pppy; the excess cost ratio between the two groups ranged

from 1.5 to 4.4. Most studies included all age groups of patients and the cost ratio was generally consistent among different age groups. The cost ratio was estimated to be approximately 2 in both studies that only included patients more than 40 years of age [76, 93]. In addition, it was reported in eight studies that additional inpatient hospital costs accounted for the majority of the excess costs in patients with DM.

Excess cost of DM complications versus no complications

The incremental costs of DM complications (Table 2.5) were reported in four studies, with different numbers of complications analysed in each. The cost ratio for a patient with DM complications to a patient without DM complications ranged from 1.9 to 2.1 [79, 91]. Three studies [54, 79, 90] did not have a matched control group, while two studies [54, 90] estimated the excess cost of three or more DM complications, resulting in higher cost ratios.

Table 2.4: Annual medical costs for individuals with and without diabetes mellitus and excess cost of individuals with diabetes mellitus

Study (year of costing)	Country	DM type	Study population	Total medical costs*[a]				
				with DM	without DM	Excess costs of DM*[a]	Cost ratio of DM to non-DM	M/NM
American Diabetes Association [74] (2007)	United States	1 & 2	All ages	US$11,744[b]	US$5,095[b]	US$6,649	2.3	NM
Balu [75] (2004)	United States	1 & 2	≥18 years of age	NR	NR	US$5,906.2	NA	NM
Bogner et al. [76] (2000 & 2001)	United States	1 & 2	≥ 65 years of age	US$10,566	US$5,450	US$5,116	1.9	NM
Currie et al. [100] (1997-2007)	United Kingdom	1 & 2	All ages	T1: £742 (US$1,180); T2: £602 (US$957.4) (1997); T1: £1,323 (US$2,104); T2: £1,080 (US$1,717.6) (2007)	T1: £254 (US$406.1); T2: £389 (US$621.9) (1997); T1: £362 (US$578.7); T2: £608 (US$972) (2007)	T1: £488 (US$773.9); T2: £213 (US$335.5) (1997); T1: £961(US$1,525.3); T2: £472 (US$745.6) (2007)	T1: 2.9; T2: 1.5 (1997); T1: 3.7; T2: 1.8 (2007)	M
Durden et al. [78] (2000 & 2005)	United States	2	All ages	US$12,423 (2000); US$12,733 (2005)	US$5,058 (2000); US$5,406 (2005)	US$7,365 (2000); US$7,327 (2005)	2.5 (2000); 2.4 (2005)	M
Esteghamati et al. [91] (2004-2005)	Tehran, Iran	1 & 2	All ages	US$191.9[b]	US$68.8[b]	US$123.1[b]	2.8	M
Köster et al. [86] (2000-2007)	Germany	1 & 2	All ages	€5,197[b] (US$6,912.5) (2000); €5,726[b] (US$7,616.1) (2007)	€2,797[b] (US$3,730.6) (2000); €3,121[b] (US$4,162.7) (2007)	€2,400[b] (US$3,181.9) (2000); €2,605[b] (US$3,453.4) (2007)	1.9 (2000); 1.8 (2007)	M
Nakamura et al. [93] (1990-2001)	Shiga, Japan	1 & 2	40-69 years of age	US$328/month	US$162/month	US$166/month	2	NM
Pohar & Johnson [84] (2001)	Canada	1 & 2	All ages	CAD$3,622 (US$3,625.9)	CAD$875 (US$877.4)	CAD$2,747 (US$2,748.5)	4.1	M

Table 2.4: Annual medical costs for individuals with and without diabetes mellitus and excess cost of individuals with diabetes mellitus

Study (year of costing)	**Country**	**DM type**	**Study population**	**Total medical costs*[a]**				
				with DM	without DM	Excess costs of DM*[a]	Cost ratio of DM to non-DM	M/NM
Tao et al. [81] (1999-2005)	United States	1	All ages	US$9,868	US$3,580	US$6,288	2.8	M
Tunceli et al. [82] (2007)	United States	1 & 2	18-65 years of age	T1: US$14,060; T2: US$8,070	T1: US$3,223; T2: US$3,853	T1: US$10,837; T2: US$4,217	T1: 4.4; T2: 2.1	M
van der Linden et al. [94] (2000-2004)	Netherlands	1 & 2	All ages	€717.43mil[bc] (US$954.2mil) (2000); €1.4bil[bc] (US$1.9bil) (2004)/yr	€275.1mil[bc] (US$367mil) (2000); €608.39mil[bc] (US$811.5mil) (2004)/yr	€442.3mil[bc] (US$587.2mil) (2000); €822.3mil[bc] (US$1.1bil) (2004)/yr	2.6 (2000); 2.4 (2004)	M
Wiréhn et al. [99] (2005)	Östergötland County, Sweden	1 & 2	All ages	€4,474[b] (US$5,950.8)	€2,504[b] (US$3,339.8)	€1,971[b] (US$2,611)	1.8	NM

* Cost converted to US-dollar; costs may not add up to exact amount due to rounding to one decimal place.
[a] Costs are per person per year, unless otherwise stated.
[b] Cost figures standardised to match age and gender distribution in the overall population.
[c] Cost figures for the entire country's population.
bil=billion; **DM**=diabetes mellitus; **M**=matched; **mil**=million; **NA**=not available; **NM**=non-matched; **NR**=not reported; **T1**=type1; **T2**=type 2; **yr**=year.

Table 2.5: Annual medical costs for individuals with and without diabetes mellitus complications and excess cost of individuals with diabetes mellitus complications

Study (year of costing)	**Country**	**DM type**	**Study population**	**Total medical costs*[a]**				
				With DM complications	without DM complications	Excess costs of DM complications*[i]	Cost ratio of DM complications to non-DM complications	M/NM
Esteghamati et al. [91] (2004-2005)	Tehran, Iran	1 & 2	All ages	US$238.7[b]	US$125.8[b]	US$112.9[b]	1.9	M
Fu et al. [79] (2004 & 2006)	United States	1 & 2	≥18 years of age	US$22,536 (MVC complication)	US$10,542 (No MVC complication)	US$11,994	2.1	NM
Tharkar et al. [90] (2009)	Chennai, India	2	All ages	US$672.6 for ≥ 3 complications	US$134.9	US$537.7	5	NM
Wang et al. [54] (2007)	(Shanghai, Beijing, Guangzhou, and Chengdu) China	2	≥18 years of age	US$4632.3 for ≥ 4 complications	US$897.4	US$3,734.9	5.2	NM

* Cost converted to US-dollar; costs may not add up to exact amount due to rounding to one decimal place.
[a] Costs are per person per year, unless otherwise stated.
[b] Cost figures standardised to match age and gender distribution in the overall population.
DM=diabetes mellitus; **M**=matched; **MVC**= macrovascular complications; **NM**=non-matched.

Discussion

Over the last three decades, numerous economic studies of diabetes have suggested that the disease is associated with a large economic burden. This present systematic review aimed to identify the evidence and summarise the findings concerning the economic burden of DM. The most notable findings in this review is that the methodology used to derive cost-of-diabetes estimates varied considerably among the 30 studies examined and that the most critical determinant of direct costs appears to be the use of inpatient care.

In our review, the cost of DM was estimated to account for 1.0% [97] to 8.7% [92] of a country's total healthcare expenditures. Ideally, the estimates of health care costs should also take into account undiagnosed DM patients. While these patients may not be receiving treatment for diabetes, they may be incurring additional healthcare costs compared to those without diabetes. The fact that people with diabetes already have complications at the time of diagnosis suggests that DM-related costs are present among the undiagnosed [101]. Therefore, overlooking these patients often leads to an underestimation of total costs that result from diabetes [77, 79, 92, 101]. According to the International Diabetes Federation, approximately 45.8% of DM patients were undiagnosed [102]. As such, the actual economic burden of DM may have been even more substantial than that estimated in the studies reviewed.

Despite the common opinion that indirect costs far exceed direct costs [20, 103], the findings of this review were less decisive. An explanation for the higher direct costs reported in eight studies may be that the costs of hospitalisation and medications have risen significantly, overshadowing indirect costs like absenteeism. In addition, in two U.S. studies, inpatient costs alone accounted for 50.0% to 75.4% of the total cost [74, 76]. This finding was consistent with other COI studies [81, 82, 86, 91, 95, 98, 103, 104], indicating that the cost of hospital care has increased markedly over recent decades. This is not surprising given the inherent high costs associated with inpatient care versus ambulatory care.

Among the studies reviewed, only eleven studies estimated the COI of DM from a societal perspective. Although COI estimates from a narrower perspective are without a doubt informative and serve a specific purpose, these studies are of limited value when the aim is to understand the economic burden of a disease from a societal perspective [20]. For example, studies taking the third-party payer perspective usually do not consider direct non-medical costs or indirect costs, as these components are not covered by an insurance plan [105].

Most of the reviewed studies used health insurance claim databases for direct medical cost estimation, an approach that is limited by its inability to capture out-of-pocket costs. In order to include these costs

and other DM-related expenses that are missed in most studies, a small number of studies also collected data from patient surveys or interviews. These retrospective and prevalence-based analyses, which were the most commonly used approaches, also have inherent limitations. These approaches often use large administrative databases, thus making it difficult to isolate the medical costs directly attributable to DM, because patients with DM typically present comorbid conditions [106, 107].

The number of direct and indirect cost categories that were considered by a study was found to have an influence on the magnitude and precision of the study's costs estimates [20]. While most studies included common costs such as inpatient, outpatient and medication costs, only a few considered costs associated with allied health, rehabilitation or nursing homecare. Studies limited to fewer categories are likely to have underestimated the actual costs of DM [20]. It is also noteworthy that most studies that dealt with patient-level data included premature mortality in estimating indirect costs, which may have contributed to the discrepancy in cost estimates and also made the comparison difficult. In order to make comparison and interpretation possible, COI studies need to be more explicit about the types of costs incorporated and how they were calculated [1, 104].

Furthermore, the reviewed studies included different population groups, which may have also influenced cost estimates. Some studies focused

on type 2 DM only, while others examined both type 1 and type 2 and/or other DM-related complications. For example, as one would expect, DM with related complications tend to be more costly than DM alone, due to the frequency and duration of hospitalisations. This difference may have also accounted for the large discrepancy in costs between the two studies [89, 90] conducted in India as the one that included DM complications resulted in higher costs.

Ettaro et al. explained that excess cost due to DM was expected to differ by age, with higher excess costs more commonly found in younger age groups [3]. However, in our findings, there was no significant difference in the cost ratio and excess costs of DM in the studies of only the elderly population compared to those that included all age groups. The reason that younger age groups did not report higher costs might be explained by better access to preventative care for DM complications or that the higher cost in the elderly population could be explained by a decrease in the use of effective healthcare resources. Based on the cost ratio, it is clear that a substantial amount of DM-attributed health expenditure and resource use is for DM complications, with most reviewed studies reporting more than a twofold increase when compared to patients with no complications. This finding highlights the importance of maintaining good glycemic control in order to prevent or reduce complications and consequently to decrease their associated costs. It was also found that the cost ratio of DM to non-DM individuals was between 2 and 3. The highest excess

cost ratio of 4.1 reported in Pohar and Johnson's study may be attributed to the study population being an ethnic minority, a group more likely to live rurally, with limited access to primary health care physicians. Consequently, these patients might only seek medical care when the disease has progressed to a later stage, which typically incurs higher overall costs.

The previous DM COI systematic review identified the highest total cost attributed to DM to be US$137.7 billion in the U.S. [108]. Similarly, our study observed the highest total cost of DM to be US$174 billion in the U.S. in 2007. This 26.0% increase in cost falls within acceptable parameters, considering inflation and rising healthcare costs across a span of 12 years. For excess costs attributed to DM, Ettaro and colleagues [3] found a cost ratio of 2 to 5 whereas in the present study, we calculated a similar cost ratio of 1.5 to 4.4. Moreover, the healthcare cost components included in Ettaro et al's study [3] were similar to components in this review, with inpatient, outpatient and medication often reported in cost-of-diabetes studies.

The present study incorporated a systematic search, a dual review of all the included studies and a comprehensive inclusion and exclusion criteria with the aim of reducing potential bias in the study selection. It should be noted, however, that the findings of this study were limited by examining only two databases and the time period of the last 5 years. It is likely that a broader search of multiple databases without

language or date restrictions would yield COI studies with different results. Furthermore, the diversity of the sampled populations and the scope of resource items included made difficult the comparison of cost estimates.

COI studies are used to educate and inform policymakers by providing fiscal information to support their decision-making processes. It is essential that COI studies be adequately designed to measure the economic burden of a disease. In addition, the design of such studies should be able to account for the variability in costs identified [1, 109, 110] and their results should be interpreted with caution [21]. Therefore, we recommend establishing agreement among researchers on the methodological principles of cost studies [111]. Moreover, guidelines or checklists need to be developed to evaluate the quality of COI analyses in order to ensure standardisation of COI studies.

Conclusion

Despite the diversity of methods used, there is a general consensus in the existing literature that DM places a significant financial burden not only on the healthcare system, but also on the individual and society as a whole. A few major findings should be highlighted. First, hospitalisation is the most important direct cost drivers. Second, a lack of standardised COI methods and study designs made direct comparisons difficult.

Understanding the magnitude of the burden of DM is important for public policymakers, that is, those who are responsible for establishing health care priorities and allocating scarce resources to yield the greatest benefits. In order to make an understanding of costs easier to obtain, guidelines for COI studies, with the goal of standardisation, should be developed.

CHAPTER THREE

Direct Medical Cost of Type 2 Diabetes in Singapore

Chapter 3 Direct Medical Cost of Type 2 Diabetes in Singapore

Introduction

Globally, the total number of people with DM is projected to rise from 171 million in 2000 to 366 million in 2030 [35]. There is a growing epidemic of diabetes mellitus, type 2 in particular, in the Asia-Pacific region [45, 46]. According to current estimates, the DM population in this region is the largest in the world, with approximately 47.3 million, which is 46% of the global burden of this disease [70]. In Singapore, as in many developed countries, DM is a growing public health problem. The prevalence of DM has risen to a 12.3% in 2013, from 8.2% in 2004 and 9% in 1998 [40, 41], surpassing other Asian countries such as Hong Kong (9.5%), Japan (7.2%) and Taiwan (5.7%) [112]. Moreover, DM is the tenth leading cause of death in Singapore, accounting for 1.7% of total deaths in 2011 [113].

Diabetes is a chronic medical condition associated with numerous complications that makes it a substantial economic burden incurred by individuals, healthcare systems and society as a whole [3]. In 2007, the global health expenditure to treat and prevent DM and its complications was estimated to be at least US$232 billion [112]. Depending on available treatments and local prevalence, the direct costs of DM consume from 2.5% to 15.0% of annual healthcare budgets [54].

Despite the large number of people with DM, the financial burden in Singapore attributable to DM has not been investigated. Because T2DM accounts for approximately 90% of DM cases and its prevalence increases with ageing, understanding the patterns of resource use and cost associated with T2DM is becoming increasingly important for policymakers and budget planners. Therefore, this study aims to identify the total direct medical cost of T2DM in Singapore and to examine the relationship between direct medical costs and individual demographic characteristics, DM interventions (exercise or diet, taking oral medications only, taking insulin only and taking both insulin and oral medications), disease control, complications and comorbidities.

Methods

Study design

This study adopted a prevalence-based 'epidemiological' approach, employing a bottom-up methodology to estimate different cost components. The prevalence approach can yield more precise estimates because it is based, at least in principle, on observed costs rather than projected ones [114]. The perspective for this study was that of the National Healthcare Group (NHG) institutions.

Data Source

This was a cross-sectional study of T2DM patients who had received care in any of the NHG institutions in 2010. The NHG is public funded and provides inpatient and ambulatory care (primary care, specialist outpatient and 24-hour emergency) services through a network of 3 acute hospitals, 1 national center, 9 primary care clinics and 3 specialty institutes serving the population in the central and western parts of Singapore. The 9 primary care clinics, also known as polyclinics, had a service load of 3.7 million attendances in 2010, which accounted for 60% of all public sector primary care attendances [115]. Data was drawn from the NHG Chronic Disease Management System (CDMS), which serves as an operational disease registry within the NHG. The CDMS was commissioned in 2007 to enhance the delivery of care for patients with DM and to facilitate greater efficiency in outcome measurement. It links key clinical data of patients with DM across the NHG healthcare cluster, including records of visits to physicians, nurses, and allied health professionals, as well as medication and laboratory test records [116]. In addition, it also includes registration and financial cost data related to the care of chronic diseases.

Patient selection

Patients with T2DM were identified using the International Classification of Diseases Ninth Revision (ICD-9-CM) diagnostic code

of 250 as primary or secondary diagnosis, or using pharmacy medication records or laboratory data in the CDMS. Diabetes complications and comorbidities were also identified using ICD-9-CM codes, while medications and laboratory data were based on inpatient and outpatient encounters at the hospital or outpatient clinics that were registered with the CDMS.

This study included patients who satisfied at least one of the following three criteria: (1) assigned ICD-9-CM code of 250; (2) attended treatment for DM for 1 year in any NHG institution; or (3) prescribed any anti-diabetic medication. Patients with type 1 DM and women with gestational diabetes were excluded.

Laboratory-derived measures related to DM

Measures for DM-related physical examinations were included and categorised as follows: (1) body mass index (BMI) (kg/m^2): <18.50 = underweight; 18.50-24.99 = normal; >25.00 = overweight and obese [117], (2) glycated haemoglobin (HbA1c) (%): ≤7.0 = good disease control; 7.1-8.0 = sub-optimal disease control; >8.0 = poor disease control, (3) low-density lipoprotein cholesterol (LDL-c) (mmol/L): <2.6 = optimal; 2.6-4.0 = near optimal; >4.0 = high, (4) urine albumin-to-creatinine ratio (UACR) (albumin/24h): <30mg = normal; 30-299mg = microalbuminuria; >300mg = macroalbuminuria [118, 119].

Estimation of costs

Direct DM-related costs were classified by the type of service, including inpatient hospitalisation, A&E and ambulatory outpatient care (physician visits, allied health visits, laboratory tests and medications). Allied health visits include foot screening, eye screening, dietary services and health education. The total medical costs were estimated by the total before-subsidy charges, which is the total medical bill before any deduction for government subsidies or insurance claims. Discounting was not required because only one-year cost was estimated. All costs reported were in Singapore currency (S$) for year 2010 prices.

The cost of inpatient care and A&E services were estimated by the total charge based on the length of stay and resources used. Any A&E visits that resulted in hospitalisation were included as inpatient care costs. Physician visits included visits to primary care clinics (polyclinics) and specialist outpatient clinics (SOC) (hospitals). Unit prices used in the estimation were equal to the standardised rate for physician visits at all NHG primary care clinics and hospitals. Therefore, costs were estimated by multiplying the number of physician visits by the unit cost of a visit. Unit prices for allied health visits, laboratory tests and medications were estimated via the same method. The cost for drugs other than anti-diabetic medications was not included. All unit costs were provided by the NHG and are in Singapore dollars. Direct non-

medical costs, such as out-of-pocket expenses and indirect or productivity costs for loss of work were not included.

Statistical methods

Healthcare cost data are often positively skewed because a relatively small proportion of patients incur extremely high costs [79, 92]. Such problems were dealt with by logarithmic transformation of the cost data [120]. Descriptive statistics (frequency, percentage, mean, median, standard deviation and 90^{th} percentile) were used for demographic information and expenditures. To identify the factors affecting total costs, a multiple linear regression model was developed to evaluate the relationship of both demographic and clinical state variables (HbA1c, DM interventions, complications and comorbidities) to the total calculated expenditure. All statistical analyses were performed using Statistical Package for the Social Science (SPSS) version 21.0 (SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics

A total of 98,592 patients in the NHG CDMS (2010) were identified as patients with DM. After applying the selection criteria and a systematic sampling, 500 patients were included in the analyses. The socio-

demographic profile of the patients is shown in Table 3.1. The patients were equally distributed between the two genders (55.4% female). The mean (±SD) age was 69.0 ± 9.4 years, and most study patients were Chinese (77.6%) and non-smokers (89.8%). Although a greater proportion of patients was overweight (42.6%), most had good disease control (44.6%), optimal LDL-c (43.2%) and normal UACR (41.2%). Of the 69.2% of DM patients who were on anti-diabetic medications, the majority used oral medications (57.2%), while only 3% were treated with insulin and the remaining 9% used both insulin and oral medications. Nephropathy (57.2%) and cardiovascular conditions (34.2%) were common DM complications among the cohort. The distributions of subgroups were similar between patients with at least one inpatient visit and those without any inpatient visit.

Annual costs of diabetes

The mean annual direct cost was S$2,034.6 (US$1.0 = S$1.3 as of 31 December 2010) [73], of which S$1,237.2 accounted for by inpatient services, S$84.2 by A&E services and S$713.2 by outpatient services (Table 3.2). Of the total healthcare expenditure, the main cost driver was inpatient costs (60.8%), while A&E services (4.1%) were only a small portion of the total costs. The major source of costs for outpatient services was physician visits, which accounted for 22.6% of the total healthcare expenditure and 64.0% of total outpatient expenditure (Figure 3.1).

Patients with at least one inpatient admission had higher mean total costs (S$8,787.8) than those who had no inpatient admission (S$690.5), with the bulk of costs resulting from inpatient services (S$7,453.3). Conversely, patients with no inpatient visit had a substantially higher proportion of overall outpatient costs.

Factors affecting the total costs

Using multiple linear regression with log transformation, the total cost of DM was significantly associated with DM interventions (taking insulin only or both oral medications and insulin) and DM-related complications (cerebrovascular, cardiovascular, and peripheral vascular diseases and nephropathy). This model explained 23.0% of the variance in costs (Table 3.3). Age, gender, race, smoking status, disease control, taking only oral medication, having retinopathy and comorbidities were not independently associated with cost. The combination of oral medications and insulin resulted in an increment in annual total cost (17.5%, $p=0.047$), while the use of only insulin led to a higher increment (53.2%, $p<0.001$) when compared with patients who were only on dietary control and healthy lifestyle advice alone. Taking the absence of complications as reference, the cost of DM was higher when complications were present except in the case of retinopathy.

Table 3.1: Socio-demographic and clinical characteristics of patients with diabetes mellitus, CDMS 2010

Characteristic	n (%)* or mean ± standard deviation		
	Overall (n=500)[1]	≥1 inpatient visit (n=83)[2]	0 inpatient visit (n=417)[3]
Individual level factors			
Age (years)	69.0 ± 9.4	71.7 ± 9.5	68.8 ± 9.3
Gender			
Female	277 (55.4)	45 (54.2)	185 (55.6)
Male	223 (44.6)	38 (45.8)	232 (44.4)
Race			
Chinese	388 (77.6)	61 (73.5)	327 (78.4)
Malay	57 (11.4)	10 (12.0)	47 (11.3)
Indian	34 (6.8)	6 (7.2)	28 (6.7)
Others	21 (4.2)	6 (7.2)	15 (3.6)
Smoking status			
Non-smoker	449 (89.8)	75 (90.4)	374 (89.7)
Smoker	51 (10.2)	8 (9.6)	43 (10.3)
Physical examination			
BMI (kg/m^2) (n=378)[1] (n=45)[2] (n=333)[3]	26.1 ± 4.7	26.0 ± 5.0	26.1 ± 4.6
Underweight	7 (1.4)	2 (2.4)	5 (1.2)
Normal	158 (31.6)	16 (19.3)	142 (34.1)
Overweight	213 (42.6)	27 (32.5)	186 (44.6)
Blood pressure (mmHg) (n=414)[1] (n=56)[2] (n=358)[3]			
Systolic	132.2 ± 14.0	134.9 ± 17.1	131.8 ± 13.4
Diastolic	70.4 ± 7.5	71.2 ± 9.3	70.3 ± 7.2
HbA1c (%) (n=441)[1] (n=73)[2] (n=368)[3]	7.3 ± 1.2	7.3 ± 1.5	7.3 ± 1.2
Good disease control	223 (44.6)	37 (44.6)	186 (44.6)
Sub-optimal disease control	134 (26.8)	19 (22.9)	115 (27.6)
Poor disease control	84 (16.8)	17 (20.5)	67 (16.1)

Table 3.1: Socio-demographic and clinical characteristics of patients with diabetes mellitus, CDMS 2010 *(continued)*

Characteristic	n (%)* or mean ± standard deviation		
	Overall (n=500)[1]	≥1 inpatient visit (n=83)[2]	0 inpatient visit (n=417)[3]
LDL-c level (mmol/L) (n=398)[1] (n=61)[2] (n=337)[3]	2.6 ± 0.8	2.7 ± 1.1	2.6 ± 0.7
Optimal	216 (43.2)	35 (42.2)	181 (43.4)
Near optimal	169 (33.8)	23 (27.7)	146 (35.0)
High	13 (2.6)	3 (3.6)	10 (2.4)
Serum creatinine (µmol/L) (n=424)[1] (n=81)[2] (n=343)[3]	102.1 ± 87.6	137.0 ± 145.4	93.9 ± 64.8
UACR (n=321)[1] (n=39)[2] (n=282)[3]			
Normal	206 (41.2)	15 (18.1)	191 (45.8)
Microalbuminuria	94 (18.8)	20 (24.1)	74 (17.7)
Macroalbuminuria	21 (4.2)	4 (4.8)	17 (4.1)
Diabetes intervention			
Diet or exercise only	154 (30.8)	27 (32.5)	127 (30.5)
Oral anti-diabetic medication only	286 (57.2)	42 (50.6)	244 (58.5)
Insulin only	15 (3.0)	8 (9.6)	7 (1.7)
Oral and insulin	45 (9.0)	6 (7.2)	39 (9.4)
Diabetes complications			
Nephropathy	286 (57.2)	63 (75.9)	223 (53.5)
Cardiovascular	171 (34.2)	49 (59.0)	122 (29.3)
Retinopathy	75 (15.0)	24 (28.9)	51 (12.2)
Peripheral vascular disease	73 (14.6)	27 (32.5)	46 (11.0)
Cerebrovascular	71 (14.2)	32 (38.6)	39 (9.4)
Diabetes comorbidity			
Dyslipidaemia	483 (96.6)	77 (92.8)	406 (97.4)
Hypertension	441 (88.2)	81 (97.6)	360 (86.3)

* Percentages may not add up to 100% due to missing values
[1] n = 500 otherwise stated in the brackets
[2] n = 83 otherwise stated in the brackets
[3] n = 417 otherwise stated in the brackets
BMI = body mass index, HbA1c = glycated haemoglobin, LDL-c = low-density lipoprotein cholesterol, UACR = urine albumin-to-creatinine ratio

Table 3.2: Direct medical costs of diabetes mellitus paid by the hospital

Costs variables	Total (S$)		%*	Mean	SD	Median	90th percentile
Overall (n=500)							
Inpatient costs		**618,622.0**	**60.8**	1,237.2	± 4,085.8	0.0	2,846.4
Accident & Emergency		**42,084.4**	**4.1**	84.2	± 277.6	0.0	300.4
Outpatient costs		**356,600.8**	**35.1**				
Physician visit	229,506.0		22.6	459.0	± 396.8	325.0	974.0
Allied health service	10,061.0		1.0	20.1	± 30.0	19.6	40.8
Laboratory tests	35,990.0		3.5	72.0	± 52.5	68.9	114.3
Medications	81,043.9		8.0	162.1	± 220.4	101.0	377.5
Total		**1,017,306.2**		**2,034.6**	**± 4,351.0**	**664.1**	**4,209.6**
≥ 1 inpatient visit (n=83)							
Inpatient costs		**618,621.0**	**84.8**	7,453.3	± 7,395.5	3,740.5	16,858.9
Accident & Emergency		**33,745.6**	**4.6**	406.6	± 550.2	301.2	722.4
Outpatient costs		**77,021.4**	**10.6**				
Physician visit	57,851.0		7.9	697.0	± 479.0	612.0	1,344.4
Allied health service	2,022.9		0.3	24.4	± 50.0	0.0	52.3
Laboratory tests	5,523.2		0.8	66.5	± 63.3	58.2	154.5
Medications	11,624.3		1.6	140.1	± 232.2	62.0	302.4
Total		**729,388.0**		**8,787.8**	**± 7,660.1**	**5,160.4**	**18,322.6**
0 inpatient visit (n=417)							
Accident & Emergency		**8,338.8**	**2.9**	20.0	± 88.9	0.0	0.0
Outpatient costs		**279,579.4**	**97.1**				
Physician visit	171,655.0		59.6	411.6	± 360.7	296.0	834.2
Allied health service	8,038.0		2.8	19.3	± 24.1	19.6	35.4
Laboratory tests	30,466.7		10.6	73.1	± 50.1	70.9	108.2
Medications	69,419.6		24.1	166.5	± 218.0	114.7	386.7
Total		**287,918.2**		**690.5**	**± 481.3**	**588.2**	**1,200.6**

* Percentages may not add up to 100% due to missing values

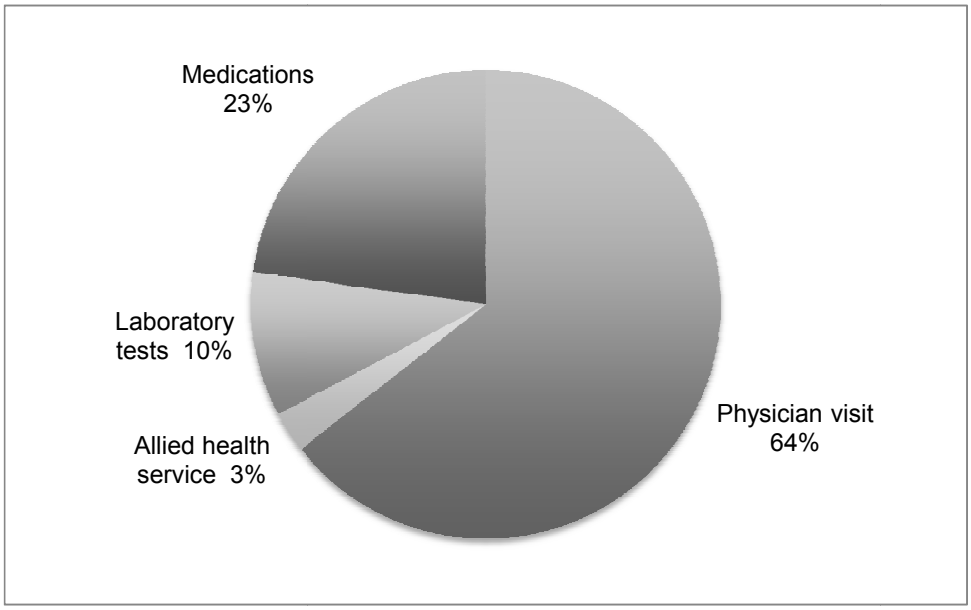

Figure 3.1: Components of outpatient costs

Table 3.3: Factors influencing the total annual cost of diabetes (n=500)*

Characteristic	β-coefficient	95% CI		P value
Individual level factors				
Age (per year increase)	0.000	-0.004	0.005	0.900
Gender				
Male (reference)				
Female	0.034	-0.047	0.114	0.412
Race				
Chinese (reference)	0.000			
Malay	0.102	-0.021	0.225	0.104
Indian	0.039	-0.120	0.198	0.632
Others	0.143	-0.050	0.336	0.146
Smoking status				
Non-smoker (reference)				
Smoker	-0.043	-0.178	0.091	0.528
Physical examination				
HbA1c (%) (n=441)				
Good disease control (reference)				
Sub-optimal disease control	0.001	-0.097	0.098	0.989
Poor disease control	0.066	-0.055	0.187	0.286
Diabetes intervention				
Diet or exercise only (reference)				
Oral medication only	0.079	-0.024	0.182	0.132
Insulin only	0.532	0.276	0.788	<0.001
Oral and insulin	0.175	0.002	0.348	0.047
Diabetes complications *(Absent reference)*				
Cerebrovascular	0.310	0.189	0.430	<0.001
Cardiovascular	0.150	0.054	0.245	0.002
Peripheral vascular disease	0.207	0.088	0.325	0.001
Nephropathy	0.123	0.005	0.240	0.041
Retinopathy	0.046	-0.070	0.161	0.436
Diabetes comorbidity				
None (reference)				
Either hypertension or dyslipidaemia	0.114	-0.101	0.328	0.298
Both hypertension and dyslipidaemia	0.071	-0.077	0.219	0.348

* n = 500 otherwise stated in the brackets

HbA1c = glycated haemoglobin

Discussion

This prevalence-based cost-of-illness study involved a large captive population with T2DM in Singapore. The analysis was based on cost and administrative data retrieved from the NHG disease registry for 2010. This is the first study to provide estimates of costs associated with diabetes care in Singapore.

The cost per patient estimate in this present study was S$2,034.6 (US$1,575.6), and this appears to be higher than the costs reported in other Asian countries. A study in India reported an estimate of US$525.5 per patient [90] while a study in China reported costs of US$1,501.7 per patient [54] for the management of DM. However, the costs reported in these studies were presented without accounting for inflation or currency differences. Notably, hospital costs reported in the American and European continents were much higher than those obtained in this study [74, 86, 95]. Despite the cost differences, inpatient costs still remained the main cost driver of the total estimated expenditure, which was also noted in the earlier DM COI studies [81, 86, 91]. Although the length of stay (LOS) was not reported in this study, often the high cost of inpatient services were often strongly correlated to LOS [121, 122], with higher LOS resulting in higher costs. This suggested that attempts to expedite services or reduce unnecessary utilisation of diagnostic tests to reduce LOS may be worthwhile in reducing overall costs.

In terms of outpatients costs, physician services contributed to the bulk of the total expenditure, and this was understandable since the growth in the number of physicians and specialists have risen over the years to meet with higher patient demands [123]. In addition, the introduction of new medical technologies and prescription drugs have also shown significant association with physician cost growth because consumers generally require physician visits to obtain diagnostic tests and prescriptions [123]. Because physicians are central to the healthcare system, efforts to contain physician spending reverberate through all healthcare services, especially since follow-ups are inevitable in chronic conditions such as DM.

Results of regression analyses generally confirmed what might have been expected based on epidemiologic evidence in the literature [54, 79, 83, 124, 125]. That is, known complications such as microvascular and macrovascular complications tend to increase the cost of care. On the contrary, comorbidities such as hypertension and dyslipidaemia did not have an association with overall cost. This result is surprising since cost-effectiveness and medication adherence studies [126-129] have reported that achieving lower levels of clinical parameters would lead to an increase in cost of care albeit increasing the quality-adjusted life years (QALY).

Patients with sub-optimal and poor disease control had lower overall costs, which seems paradoxical. One might expect that DM patients

with higher HbA1c, would require more health services. This may be an indicator of barriers to healthcare and/or poor diabetes self-management resulting in lower healthcare costs when compared to patients with good disease control. The importance of managing DM to prevent or delay complications requires effort [130] and good control of DM results in long-term cost savings due to fewer complications [131]. Furthermore, the use of insulin only or both insulin and oral medications were found to be associated with higher costs. Consistent with other studies, the most expensive component of total outpatient costs after physician costs were medications [74, 85, 86, 91]. This rise in cost indicated a growth in the consumption of prescription medications, which could be due to more patients being compliant with their medications. This compliance may result in better healthcare outcomes and reduce the need for physician visits [132, 133], which could ultimately lead to a net decrease in overall healthcare cost.

As a prevalence-based cost-of-illness study, the strength of this study lies in that all DM cases were included from a specified year, regardless of whether or not they were diagnosed before or during that year. This breadth allows for a cross-section of patients in various stages of the illness, since different severities of DM are associated with different costs. However, several limitations of this study should be noted. First, data was drawn from a healthcare database, hence relied on the accuracy and completeness of the records. The NHG CDMS has, however, been used in several studies and is recognised for

providing well-validated and comprehensive data [115, 134]. Second, patients with undiagnosed diabetes as well as indirect/intangible costs and out-of-pocket expenses were not included, which has likely resulted in an underestimation of the true cost of diabetes. Lastly, the study population was relatively small and limited to the public healthcare sector in Singapore.

Conclusion

This study provided a comprehensive cost analysis of expenditures incurred in the treatment of the DM population in Singapore. The results indicated that both medications and DM complications were strong determinants of costs. As the prevalence of DM in Singapore continues to grow in the years to come, coupled with both improved medical treatment on the one hand and the increasing prevalence of obesity on the other, diabetes will continue to be a heavy burden on health budgets. Hence, as observed from the present findings, knowledge of the economic burden related to each T2DM complication and what drives cost can be useful in health-system reform that seeks to minimise the long-term economic burden of this growing epidemic.

CHAPTER FOUR

Direct Medical Cost of Stroke in Singapore

Chapter 4 Direct Medical Cost of Stroke in Singapore

Introduction

Globally, stroke is the second most common cause of death and one of the main causes of long term disability [135]. Approximately 16 million first-occurrence strokes occur around the world per year, accounting for 5.7 million deaths [36]. In 2010, stroke-related disability was judged to be the third most common cause of reduced DALYs [136]. Much of the available epidemiologic data on stroke come from Europe, the United States and Australia, with little data from countries in Asia other than China, India and Japan [50]. In Singapore, stroke is the fourth leading cause of death, accounting for 9.0% of total deaths in 2013. It has a prevalence of 3.7% and an incidence of 1.8 per 1,000 person-years and it is among the top 10 causes of hospitalisation [42, 43].

Stroke is a debilitating and costly chronic medical condition. Worldwide, stroke consumes about 2–4% of total healthcare expenditure, and in developed countries stroke accounts for more than 4% of direct healthcare costs [56]. The total annual costs have been variously estimated at US$40 billion in the United States [57], AUS$1.3 billion in Australia [58], and £8.9 billion in the United Kingdom [59]. A study conducted in Singapore in 1996 estimated the mean direct cost for hospital care to be S$7,547, with ward charges accounting for the majority of the total cost [137].

With a rapidly aging population, the number of elderly citizens in Singapore will likely triple to 900,000 by 2030, and a consequent increase in the prevalence of stroke is expected [138, 139]. It is timely to examine the factors influencing the cost of stroke in order to provide local information to the government, healthcare providers, and policymakers who are responsible for establishing healthcare priorities and taking advantage of potential savings. Their decisions will ultimately dictate how the economic burden of a disease is distributed.

Therefore, this study aims to identify the total direct medical cost of the four main stroke types in Singapore: (1) ischaemic stroke (IS), (2) subarachnoid haemorrhage (SAH), (3) intracerebral haemorrhage (ICH) and (4) transient ischaemic attack (TIA) and also to examine the relationship between the total estimated costs and individual demographic characteristics, type of stroke, length of post-stroke period, complications and comorbidities.

Methods

Study design

This study adopted a prevalence-based epidemiological approach, employing a bottom-up methodology to estimate different cost components. The prevalence approach can yield more precise estimates because it ascertains the current economic burden of a

disease rather than projected ones [114] and is commonly used in illnesses that produce long-term sequelae [140]. The perspective for this study was that of the NHG institutions.

Data source

This was a cross sectional study of stroke patients who had received care in any of the NHG institutions between January 1, 2006 and December 31, 2012. The NHG is an integrated public healthcare delivery system which consists of 3 acute hospitals, 1 national center, 9 primary care clinics and 3 specialty institutes. The NHG provides primary care, inpatient, specialist outpatient and 24-hour emergency services for the population in the central and western parts of Singapore [116]. The 9 primary care clinics, also known as polyclinics, are a government primary care provider organisation with a service load of 3.7 million visits in 2010, which accounted for 60% of the entire public sector [115]. Data was drawn from the NHG CDMS, which was commissioned in 2007 with the aim to build a registry that helps to provide seamless care for patients with chronic diseases and to facilitate greater efficiency in outcome measurement. The system links administrative and key clinical data of patients with stroke within the NHG healthcare cluster, including physician visits, medication and laboratory test records [116, 141].

Patient selection

The ICD-9-CM was used to identify patients with stroke. The patients were selected if found to have both diagnostic codes between 430-436 as a primary or secondary diagnosis, in addition to having pharmacy medication records and laboratory data available in the CDMS. Frequently encountered stroke complications and comorbidities were also identified using ICD-9-CM codes, while medications and laboratory data were extracted based on inpatient and outpatient encounters registered with the CDMS.

This study included patients who were at least 21 years of age and had an ICD-9-CM code between 430 and 436 (SAH=430; IS=431, 433, 434; ICH=432; TIA=435; unspecified=436) or attended treatment for stroke in any NHG institution. Patients with stroke were stratified by stroke types: IS, SAH, ICH, and TIA. Patients were also further divided into two groups (acute and prevalent). They were considered acute if they had a stroke onset in the year 2011 and prevalent if they had a stroke onset between 2006-2010. To determine the date of stroke onset, only the first hospitalisation for each acute patient was included, and when prevalent patients presented with multiple strokes during the study's time frame, the most recent stroke type other than TIA was selected for analysis. In addition, patients needed to have at least one record in the CDMS in the year 2012 if acute and the year 2013 if prevalent to ensure survival post stroke. Patients with strokes other

than IS, SAH, ICH and TIA were excluded. To ensure a representative sample of different types of stroke, 150 IS patients, 50 SAH patients, 100 ICH patients, and 50 TIA patients were randomly selected for acute and prevalent groups, giving a total of 700 patients selected for analysis.

Resource use and cost estimation

Direct stroke-related costs were classified by the type of service, which included inpatient hospitalisation, A&E and ambulatory outpatient care (physician visits, laboratory tests and medications). The total medical costs were estimated using the total before-subsidy charges, which is the total medical bill before any deductions that result from government subsidies and insurance claims. Discounting was not required because only one-year cost was estimated. Costs estimated were for a period of one year; all resources utilised for the year 2012 were reported in Singapore currency (S$) using year 2012 prices.

Costs of inpatient care and A&E services were estimated by the total charge, which was determined by the length of stay and the resources used. A&E visits that resulted in hospitalisation were included as inpatient costs. Physician visits included visits to primary care clinics (polyclinics) and SOC (hospitals). The standardised rate at all NHG primary care clinics and hospitals was used as the unit costs for physician visits. Costs were estimated by multiplying the number of

physician visits by the unit cost of a visit. Costs of medications and laboratory tests were estimated via the same method. Since there is no stroke-specific medications or laboratory tests, the most commonly prescribed medications and ordered laboratory tests for stroke patients were included in the cost estimation. All unit costs were provided by the NHG and were in Singapore dollars. Direct non-medical costs, such as out-of-pocket expenses and indirect or productivity costs for loss of work were not included in this study.

Statistical analysis

Logarithmic transformation of the cost data was performed since healthcare cost data are often positively skewed due to a relatively small proportion of patients incurring extremely high costs [142, 143]. Descriptive statistics (frequency, percentage, mean, median, standard deviation and 90^{th} percentile) were used to present costs and patients' demographics. Multiple linear regression analyses were performed to determine the predictors of the total costs. All statistical analyses were performed using SPSS version 22.0 (SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics

A total of 8,230 (2,144 acute; 6,086 prevalent) stroke patients in the NHG CDMS (2006-2012) were identified as stroke patients. After random sampling, 700 patients were included in the analyses, of which half were acute and half prevalent. The socio-demographic profile of the patients is shown in Table 4.1. The overall patient sample was equally distributed between the two genders (55.1% male), and the mean (±SD) age was 62.7 ± 13.5 years. The mean (±SD) length of post-stroke period was 1.7 ± 1.5 years and most study patients were Chinese (83.1%). Of the 350 prevalent patients, only 12.3% had one or more inpatient visits compared to 93.1% in the acute group. Urinary tract infection (UTI) (19.0%) and pneumonia (6.0%) were the most common stroke complications among the cohort. Only 9 (1.3%) patients had retinopathy, while dyslipidaemia (85.6%), hypertension (76.6%) and DM (32.1%) were common comorbidities.

Among the four types of stroke, men comprised slightly more than half of the patients in the IS (60.0%), ICH (62.0%) and TIA (55.0%) groups, while only 27% of the patients were male in the SAH sample. On average, patients with SAH tended to be younger than those with the other types of stroke and the majority of the patients were Chinese in all stroke groups. The mean length of post-stroke period was also similar amongst the four stroke types. Similar to the overall patient sample, patients with different stroke types had UTI and pneumonia as common complications, while dyslipidaemia, hypertension and DM were common comorbidities.

Table 4.1: Socio-demographic and clinical characteristics of patients with stroke, CDMS 2006-2012

Characteristic	n (%)* or mean ± standard deviation											
	Overall (n=700)		IS (n=300)		SAH (n=100)		ICH (n=200)		TIA (n=100)			
Age (years)	62.7 ± 13.5		65.7 ± 13.6		55.4 ± 13.9		61.7 ± 11.9		62.8 ± 13.1			
Gender												
Male	386	(55.1)	180	(60.0)	27	(27.0)	124	(62.0)	55	(55.0)		
Female	314	(44.9)	120	(40.0)	73	(73.0)	76	(38.0)	45	(45.0)		
Race												
Chinese	582	(83.1)	239	(79.7)	82	(82.0)	178	(89.0)	83	(83.0)		
Malay	65	(9.3)	36	(12.0)	11	(11.0)	9	(4.5)	9	(9.0)		
Indian	35	(5.0)	18	(6.0)	4	(4.0)	8	(4.0)	5	(5.0)		
Others	18	(2.6)	7	(2.3)	3	(3.0)	5	(2.5)	3	(3.0)		
Post-stroke period (years)	1.7 ± 1.5		1.6 ± 1.4		1.7 ± 1.5		1.7 ± 1.5		1.7 ± 1.5			
Length of stay (days)												
Acute (n=350)	27.4 ± 39.7		23.0 ± 30.7		39.3 ± 44.1		39.0 ± 51.4		4.9 ± 7.8			
Prevalent (n=350)	1.9 ± 9.4		2.3 ± 9.2		1.0 ± 3.1		2.5 ± 13.3		0.7 ± 3.0			
≥ 1 inpatient visit												
Acute (n=350)	326	(93.1)	141	(47.0)	50	(50.0)	99	(49.5)	36	(36.0)		
Prevalent (n=350)	43	(12.3)	18	(6.0)	7	(7.0)	14	(7.0)	4	(4.0)		
Stroke complications												
Urinary tract infection	133	(19.0)	48	(16.0)	35	(35.0)	44	(22.0)	6	(6.0)		
Pneumonia	42	(6.0)	15	(5.0)	9	(9.0)	16	(8.0)	2	(2.0)		
Acute myocardial infarction	17	(2.4)	6	(2.0)	0	(0.0)	5	(2.5)	6	(6.0)		
Deep vein thrombosis	8	(1.1)	3	(1.0)	2	(2.0)	2	(1.0)	1	(1.0)		
Gastrointestinal tract bleeding	8	(1.1)	4	(1.3)	1	(1.0)	3	(1.5)	0	(0.0)		
Decubitus ulcer	3	(0.4)	1	(0.3)	0	(0.0)	2	(1.0)	0	(0.0)		

Table 4.1: Socio-demographic and clinical characteristics of patients with stroke, CDMS 2006-2012 *(continued)*

Characteristic	n (%)* or mean ± standard deviation											
	Overall (n=700)		IS (n=300)		SAH (n=100)		ICH (n=200)		TIA (n=100)	
Stroke comorbidities										
Dyslipidaemia	599	(85.6)	291	(97.0)	56	(56.0)	155	(77.5)	97	(97.0)
Hypertension	536	(76.6)	247	(82.3)	41	(41.0)	174	(87.0)	74	(74.0)
Diabetes mellitus	225	(32.1)	120	(40.0)	11	(11.0)	60	(30.0)	34	(34.0)
Chronic kidney disease	102	(14.6)	56	(18.7)	4	(4.0)	27	(13.5)	15	(15.0)
Ischaemic heart disease	99	(14.1)	48	(16.0)	5	(5.0)	24	(12.0)	22	(22.0)
Atrial fibrillation	68	(9.7)	44	(14.7)	3	(3.0)	13	(6.5)	8	(8.0)
Heart failure	38	(5.4)	19	(6.3)	3	(3.0)	12	(6.0)	4	(4.0)
Peripheral vascular disease	27	(3.9)	17	(5.7)	1	(1.0)	4	(2.0)	5	(5.0)
Retinopathy	9	(1.3)	7	(2.3)	0	(0.0)	2	(1.0)	0	(0.0)

* Percentages may not add up to 100% due to rounding

Annual costs of stroke

The mean annual direct cost of stroke was estimated to be S$12,473.7 (US$1.0 = S$1.2 as of 31 December 2012) [73], of which S$11,672.5 was for inpatient services, S$188.7 for A&E services and S$612.5 for outpatient services (Table 4.2). Of the total healthcare expenditure, the main cost driver was inpatient costs (93.6%), while A&E services (1.5%) were only a small portion of the total costs. The major source of costs for outpatient services was physician visits, which accounted for 4.9% of the total healthcare expenditure and 75.0% of total outpatient expenditure.

Patients with SAH (S$22,990.9) were the most costly on average, followed by patients with ICH (S$16,600.6), IS (S$9,138.5) and TIA (S$3,708.5). The mean costs were 4.1 times higher than median cost estimates for patients with SAH and 4.4 times for patients with ICH, demonstrating that a minority of patients with extremely high costs had a substantial influence on the mean estimates. The mean costs for patients with IS and TIA were less influenced by outliers. Inpatient costs were higher in the IS (S$8,303.5), SAH (S$22,464.9) and ICH (S$15,702.3) groups when compared to the TIA group (S$2,927.9), indicating a higher resource consumption in those groups. Conversely, patients with TIA had a higher proportion of resource consumption for outpatient services than the other stroke groups. Outpatient costs were consistent across the four stroke groups, with physician services

accounting for the majority of total expenditure, followed by laboratory tests and medications (Table 4.2).

Healthcare expenditure across all services was substantially higher in acute patients than prevalent patients. The mean annual costs were S$22,721.3 (acute) and S$2,226.2 (prevalent), of which 95.5% and 73.5%, respectively, were accounted for by inpatient services. Outpatient services were more utilised in the prevalent arm, which is evident when comparing the proportion of outpatient costs to the total costs in each group. Although the proportion of outpatient costs in physician services, laboratory tests and medications were similar in both groups, the mean total physician visit cost was higher in acute patients (Table 4.3).

Predictors of total costs

Cost predictors were investigated using multiple linear regression with log transformation. A greater total cost of stroke was significantly associated with stroke type (IS, SAH and ICH), shorter post-stroke period, more than one stroke complications and a greater number of comorbidities. This model explained 61.0% of the variance in costs (Table 4.4). Compared with patients with TIA, the mean annual total cost of those with IS was 18.2% higher ($p=0.005$), while the increase in the total costs of patients with SAH (41.0%, $p<0.001$) and ICH (29.2%, $p<0.001$) was even greater. Age, gender, and race were not

independently associated with the total cost.

Table 4.2: Direct medical costs incurred by stroke type at different site of care

Site of care	*IS (n=300)*	*SAH (n=100)*	*ICH (n=200)*	*TIA (n=100)*	*OVERALL (n=700)*
Inpatient					
Cost (S$)	2,491,036.8	2,246,490.7	3,140,451.2	292,791.0	8,170,769.7
Percentage of total cost (%)*	90.9	97.7	94.6	79.0	93.6
Mean	8,303.5	22,464.9	15,702.3	2,927.9	11,672.5
SD	± 15,742.1	± 34,614.8	± 43,657.7	± 7,228.2	± 29,374.2
Median	2,286.0	5,324.4	2,549.4	1,232.7	2,013.9
90th percentile	23,719.2	59,640.1	40,987.3	4,508.4	33,877.7
Accident & Emergency					
Cost (S$)	55,553.2	12,892.3	41,599.3	22,012.6	132,057.4
Percentage of total cost (%)*	2.0	0.6	1.3	5.9	1.5
Mean	185.2	128.9	208.0	220.1	188.7
SD	± 284.3	± 211.8	± 302.5	± 375.5	± 296.2
Median	58.7	0.0	111.0	128.0	0.0
90th percentile	538.7	394.9	633.7	588.2	523.5
Outpatient					
Cost (S$)	194,960.1	39,702.4	138,061.6	56,043.7	428,767.8
Percentage of total cost (%)*	7.1	1.7	4.2	15.1	4.9
Mean	649.9	397.0	690.3	560.4	612.5
SD	± 620.2	± 534.7	± 1,396.6	± 439.9	± 892.8
Median	482.7	225.3	383.3	485.7	415.8
90th percentile	1,469.4	914.0	1,336.8	1,227.9	1,255.0

Table 4.2: Direct medical costs incurred by stroke type at different site of care *(continued)*

Site of care	*IS (n=300)*	*SAH (n=100)*	*ICH (n=200)*	*TIA (n=100)*	*OVERALL (n=700)*
Outpatient physician visits					
Cost (S$)	134,753.1	35,213.8	115,355.9	38,726.9	324,049.7
Percentage of total outpatient cost (%)*	69.1	88.7	83.6	69.1	75.6
Mean	449.2	352.1	576.8	387.3	462.9
SD	± 443.4	± 519.8	± 1,357.1	± 300.6	± 816.0
Median	306.7	209.3	277.8	315.0	281.6
90th percentile	1,013.8	670.7	1,064.4	822.5	912.0
Outpatient laboratory tests					
Cost (S$)	41,823.7	2,816.9	15,934.3	11,271.0	71,845.9
Percentage of total outpatient cost (%)*	21.5	7.1	11.5	20.1	16.8
Mean	139.4	28.2	79.7	112.7	102.6
SD	± 196.5	± 57.5	± 107.5	± 135.0	± 156.2
Median	88.6	0.0	59.3	81.8	71.7
90th percentile	355.3	123.1	193.7	277.5	245.8
Outpatient medications					
Cost (S$)	18,383.3	1,671.8	6,771.4	6,045.8	32,872.2
Percentage of total outpatient cost (%)	9.4	4.2	4.9	10.8	7.7
Mean	61.3	16.7	33.9	60.5	47.0
SD	± 101.6	± 60.6	± 84.7	± 112.3	± 95.1
Median	29.5	0.0	5.9	27.0	14.7
90th percentile	154.4	6,771.4	80.7	126.6	122.1
TOTAL COST					
Cost (S$)	2,741,550.1	2,299,085.4	3,320,112.1	370,847.4	8,731,594.9
Mean	9,138.5	22,990.9	16,600.6	3,708.5	12,473.7
SD	± 16,095.6	± 34,748.5	± 43,755.2	± 7,479.4	± 29,517.2
Median	3,109.3	5,601.7	3,801.1	1,888.3	2,929.2
90th percentile	26,213.1	60,193.7	41,368.2	5,619.3	35,102.1

* Percentages may not add up to 100% due to rounding

Table 4.3: Direct medical costs incurred by patient type at different site of care

Site of care	*Acute (n=350)*	*Prevalent (n=350)*
Inpatient		
Cost (S$)	7,598,109.3	572,660.5
Percentage of total cost (%)*	95.5	73.5
Mean	21,708.9	1,636.2
SD	± 38,419.7	± 7,075.2
Median	9,118.6	0.0
90th percentile	50,220.4	3,280.0
Accident & Emergency		
Cost (S$)	108,898.0	23,159.4
Percentage of total cost (%)*	1.4	3.0
Mean	311.1	66.2
SD	± 335.4	± 182.0
Median	245.2	0.0
90th percentile	683.7	273.0
Outpatient		
Cost (S$)	245,433.6	183,334.2
Percentage of total cost (%)*	3.1	23.5
Mean	701.2	523.8
SD	± 813.0	± 959.1
Median	477.3	385.7
90th percentile	1,522.1	899.9
Outpatient physician visits		
Cost (S$)	190,299.0	133,750.7
Percentage of total outpatient cost (%)*	77.5	73.0
Mean	543.7	382.1
SD	± 696.1	± 914.4
Median	340.9	234.6
90th percentile	1,237.5	624.9
Outpatient laboratory tests		
Cost (S$)	39,109.3	32,736.6
Percentage of total outpatient cost (%)*	15.9	17.9
Mean	111.7	93.5
SD	± 187.1	± 117.0
Median	34.4	82.9
90th percentile	330.1	193.9
Outpatient medications		
Cost (S$)	16,025.4	16,846.8
Percentage of total outpatient cost (%)*	6.5	9.2
Mean	45.8	48.1
SD	± 105.4	± 83.8
Median	10.3	18.8
90th percentile	113.6	126.6
TOTAL COST		
Cost (S$)	7,952,440.9	779,154.1
Mean	22,721.3	2,226.2
SD	± 38,490.9	± 7,269.5
Median	9,938.0	444.6
90th percentile	53,080.3	4,925.8

* Percentages may not add up to 100% due to rounding

Table 4.4: Factors influencing the total annual cost of stroke (n=700)

Characteristic	β-coefficient	95% CI		P value
Individual level factors				
Age (per year increase)	0.001	-0.003	0.004	0.634
Gender				
Male (reference)				
Female	-0.045	-0.133	0.042	0.307
Race				
Chinese (reference)				
Malay	0.083	-0.063	0.228	0.265
Indian	0.013	-0.178	0.204	0.891
Others	0.117	-0.147	0.380	0.385
Stroke type				
TIA (reference)				
IS	0.182	0.055	0.308	0.005
SAH	0.410	0.243	0.577	<0.001
ICH	0.292	0.157	0.427	<0.001
Post-stroke period				
Acute <1 year (reference)				
Prevalent 1 to 3 years	-1.230	-1.326	-1.133	<0.001
Prevalent >3 years	-1.411	-1.519	-1.303	<0.001
Stroke complications				
None (reference)				
1 complication	0.103	-0.005	0.211	0.061
>1 complications	0.207	0.004	0.410	0.045
Stroke comorbidities				
Number of comorbidities (per 1 increase)	0.055	0.022	0.089	0.001

Discussion

This prevalence-based COI study involved a large captive population with stroke in Singapore. The analysis was based on cost, administrative and clinical data retrieved from the NHG disease registry from 2006-2012. This is the first study to provide estimates of the distribution of costs among the different stroke types as well as costs among acute and prevalent patients in both inpatient and ambulatory care in Singapore.

The cost per patient estimate in the present study was S$12,473.7 (US$10,190.3), and this appears to be higher than those reported in other Asian countries. Two studies in Korea reported an estimate of approximately KRW$8 million per patient [144, 145], while in China it costs CNY$30,438.3 per patient for the management of stroke [143]. Notably, direct medical costs reported in the American [146] and European [147, 148] continents were much higher than those estimated in this study. The comparison of mean total cost with other studies was further hindered by the estimation of only first year (acute) or hospitalisation costs and the limited number of stroke types included in most studies.

Despite the differences in total costs estimated, inpatient costs remain the main cost driver, which is consistent with previous stroke COI studies [58, 143, 149]. The high costs in inpatient services are often

strongly correlated to LOS [121, 122], where a higher LOS results in higher costs. Previous studies [150, 151] have also reported that having complications was associated with a significant increase in the LOS. With the many complications accompanying a stroke, it is inevitable that inpatient care dominates the total healthcare expenditure. This fact underlines the need for effective preventative measures and careful treatment of these complications. Furthermore, early mobilisation and careful monitoring of clinical parameters seem to be beneficial as well [152, 153]. In terms of outpatient costs, physician services contributed to the bulk of the total expenditure, which is understandable since the growth in the number of physicians and specialists in outpatient care has risen over the years to meet patient demands, resulting in an increase in outpatient physician visits. One study [154] proposed increasing the case load of physicians, which provides opportunities for physicians to develop cost-effective as well as technically effective medical treatment skills to deal with the high demands. This may also make them more savvy in coordinating the various treatment elements and discharge planning, leading to a reduction in costs related to care content. As outpatient physicians are central to the healthcare system, efforts to contain physician spending will have positive effects on all healthcare services.

As in previous studies, patients with SAH were younger, have lower outpatient costs and higher overall costs compared with other cerebrovascular diseases [155-158]. This young age could lead to

greater lifetime costs, due to long-term management of the disease and loss of productivity costs [57, 159, 160], which raises a concern for the national economy because of the diminishing workforce. On the other hand, IS were more common in the elderly, in particular, in individuals above the age of 65 [161]. Due to the non-disabling nature of TIA, these patients are more commonly managed as outpatients than inpatients [162] and results in lower overall healthcare costs, which was further validated in the regression analysis. The general consensus was that haemorrhagic strokes on the whole were more costly than IS and TIA [149, 163, 164], given the frequent need for surgery and intensive monitoring with high levels of subsequent morbidity [146, 165, 166].

Cost of stroke within the first year of occurrence is concerning, with healthcare use being substantially higher when compared to prevalent patients [59, 147, 167]. This vast disparity was mainly due to inpatient costs dominating the burden for acute cases with high ward charges and diagnostic tests. The severity of the disease coupled with multiple follow-ups at outpatient clinics could also be possible explanations [122, 147]. The present study's cost estimates for the acute phase are noticeably much higher than those obtained by three [137, 168, 169] previous studies done in Singapore. Chow et al [168] estimated an average cost of S$6,783, while S$7,547 was reported by Venketasubramanian et al [137] and S$2,410.8 by Saxena et al [169]. However, it should be noted that these earlier studies only estimated

hospitalisation costs. Furthermore, Chow et al included only patients with IS, while Saxena et al estimated costs in a community hospital setting. The heavy inpatient focus of hospitals is not cost-effective for the management of chronic diseases. Data for diseases such as asthma and congestive heart failure [170, 171] clearly indicate that cost savings come from what happens over the long term outside of hospitals to prevent acute episodes from occurring [172], and much of these savings may have been the result of empiric identification of barriers to efficient diagnosis and management as well as more aggressive discharge planning.

The results of regression analyses generally confirmed what might have been expected based on epidemiologic evidence in the literature. That is, complications and comorbidities tend to increase the cost of care. A study by O'Brien and colleagues [173] found that complications that are initially relatively low in cost could progress to become more costly in the advanced stages due to higher resource consumption. For example, stroke patients with multiple complications and/or comorbidities would naturally require medications for each condition, further driving up the healthcare cost of stroke survivors [174]. As such, it may be that efforts to curb stroke complications would not only result in a decrease in medication costs but also decreased costs at all sites of care (inpatient and outpatient), due to the decline in LOS as well as number of follow-ups. Thus, decreasing the rate of people developing

complications and/or comorbidities through patient-targeted disease-management could be beneficial in reducing overall healthcare costs.

This study is not without limitations. First, data was drawn from a healthcare database and, as such, relied on the accuracy and completeness of the records. However, the NHG CDMS has been used in several studies and is recognised as providing well-validated and comprehensive data [115, 134]. The integration of both administrative and clinical data allows a detailed characterisation of the patient at the index date and was also useful in running prediction models. Second, patients with stroke other than IS, SAH, ICH and TIA, along with indirect and intangible costs and out-of-pocket expenses were not examined in this study. These limits in scope have likely underestimated the true cost of stroke. In addition, due to the lack of data, stroke severity, which is an important predictor of costs, was omitted from the analysis. Third, the study population was limited to the public healthcare sector in Singapore. Nevertheless, the strength of this prevalence-based COI study lies in that all cases of stroke are included for a specified year, which allows for a cross-section of patients in various stages of the illness.

Conclusion

This study provides a comprehensive cost analysis for the stroke population in Singapore. The results indicate that stroke type, length of

post-stroke period as well as stroke complications and comorbidities are significant determinants of the total costs. With an aging population, the prevalence of stroke in Singapore will continue to grow in the years to come, resulting in a heavy burden on health budgets. Hence, it is important to understand what drives costs in order to further underscore the need for effective preventive therapies, timely critical care and well-designed rehabilitation programs to contain stroke-related healthcare costs and to enhance the quality of life in our aging society.

CHAPTER FIVE

Cost of Osteoporotic Fracture in Singapore

Chapter 5 Cost of Osteoporotic Fractures in Singapore

Introduction

Osteoporosis is a bone condition closely related to advancing age that is characterised by reduced bone mass and microarchitectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fractures [175-177]. It is considered a serious public health concern, with an estimated 200 million people worldwide suffering from this disease [178]. Osteoporosis-related fractures are associated with a high degree of morbidity and mortality [179]. The average lifetime risk of an elderly over the age of 50 to experience osteoporotic fracture has been estimated at 40-50% for women and 13-22% for men [180]. In 2000, 9 million osteoporotic fractures occurred worldwide, including 1.6 million hip fractures, 1.7 million forearm fractures, and 1.4 million clinical vertebral fractures [38, 39]. In Singapore, hip fracture incidence rates have risen 1.5-fold for men and 5-fold for women since the 1960s. The age-adjusted hip fractures rates among women over the age of 50 years are about 402 per 100,000 females and this figure is now among the highest in Asia [47-49].

Osteoporotic fractures are a chronic condition and one of the most common causes of disability, incurring substantial costs in many regions of the world. The annual costs of all osteoporotic fractures have been variously estimated to be US$20 billion in the United States

[60], €30 billion in the European Union [61] and AU$1.8 billion in Australia [62]. A study conducted in Singapore in 2001 estimated the mean hospitalisation cost for patients with hip fractures treated surgically to be S$10,515 [181].

By 2050, the percentage of the population aged 60 years and above in Singapore is projected to increase to 38% [182]. With an aging population, the number of hip fractures per year is projected to increase from 1,300 in 1998 to 9,000 by 2050 [48]. Despite the large number of people affected by osteoporosis, no previous study in Singapore has compared the costs of patients with acute to those with prevalent osteoporotic fractures or examined these groups indirect costs in Singapore. It is timely to estimate current various costs of osteoporotic fractures in the local context so as to develop policies, allocate resources appropriately and justify intervention programs resulting in potential financial savings.

The present study aims to identify the total direct and indirect costs of osteoporotic fractures in Singapore from both the hospital's and patient's perspectives, including cost comparisons between patients with acute and those with prevalent osteoporotic fractures.

Methods

Study design

This study adopted a prevalence-based approach, employing a bottom-up methodology to estimate different cost components. The prevalence approach can yield more precise estimates because it ascertains the current economic burden of a disease rather than projected ones [114]. The perspective for this study was that of the National University Hospital (NUH) and patients with osteoporotic fractures.

Data collection

A prospective observational study of patients with osteoporotic fractures was conducted from late July 2013 to January 31, 2014 over a 6-month period. The NUH is a 997-bed public tertiary hospital serving more than 670,000 outpatients and 59,000 inpatients in 2010 [183].

Data regarding resource use was collected using interviewer-administered questionnaires at baseline (i.e. the date of interview) and at a 3-month follow-up to minimise recall bias. The interviews were conducted at the department of orthopaedics of NUH, which includes inpatient wards, outpatient specialist clinics, the A&E department and other relevant clinics (i.e. the radiological department). The questionnaires (See Appendix I and II) used were adapted from

existing instruments developed by the collaborating NUH rheumatologist and a corresponding author of a COI study conducted in Singapore. Either the English or Chinese version of the questionnaire was administered, depending on the patient's preference. At baseline, patients' demographics, clinical characteristics and resources used for that particular visit were obtained. Patients were then asked to take note week by week of all contacts, receipts or bills they had with or from the healthcare system for the next 3-months. At the 3-month follow-up, information on resource use since the last visit was collected. Patient-reported information at baseline and follow-ups were primarily collected via interviews in connection with the hospital visits related to the fracture event. If the interview could not be conducted in relation to the hospital visit, the information were collected via a telephone interview. In circumstances where the patient was unable to respond to the questions accurately, the questionnaires were given to a "proxy-responder" (i.e. a person in close contact with the patient).

Patient selection

To be included in the study, patients were required to have a bone mineral density (BMD) scan or relevant X-ray examinations to ensure that their fractures were low-trauma (i.e. sustained from standing height or less) and fulfill the following criteria: (1) above 50 years of age, (2) vertebral column, hip, humerus, wrist or other fragility fracture (except

skull, below ankle and distal to the wrist) and (3) able to ambulate with or without aid before fall (i.e. not wheelchair or bed bound). Eligible patients were identified through visits to the department of orthopaedics (inpatient ward and outpatient specialist clinics), A&E department or were identified by the case finding approach at other relevant clinics. This was an Institutional Review Board-approved study and written informed consent was obtained for each patient.

The consequences related to fractures can be divided into an acute incident phase and a post-prevalent fracture phase. Patients were categorised as being in the acute phase if the fracture occurring ≤ 4 weeks prior to the interview was their first fracture, while patients who had their present fracture for over one year were considered prevalent. Patients with a pathological fracture due to metastasis or patients seeking care for multiple fractures simultaneously were excluded. Patients with apparent cognitive impairment that would have prevented them from answering the survey questions accurately were also excluded.

Estimation of direct medical costs

Direct medical cost was classified by the type of service, which included inpatient hospitalisation, A&E and ambulatory outpatient care (physician visits, laboratory tests, rehabilitations and medications). The total costs were estimated using the total before-subsidy and after-

subsidy charges, which is the total medical bill before and after any deductions that result from general government subsidies. Subsidies from government programs such as Medisave, Medifund, MediShield and ElderShield as well as any private insurance claims, individual or employer-provided were not taken into consideration.

Costs of inpatient care and A&E services were estimated by the total charge, which was determined by the length of stay and the resources used. A&E visits that resulted in hospitalisation were included as inpatient costs. Physician visits included visits to primary care clinics (polyclinics) and SOC (hospitals) and were estimated based on the receipts or bills provided by the patient. Laboratory tests such as X-rays, magnetic resonance imaging (MRI), BMD or blood tests and rehabilitation services were estimated via the same method. Physician visits that included laboratory tests that were done in tandem during the same visit were included as physician visit costs because receipts were generated based on a pre-programmed government subsidy deduction of the total charge for that visit. Rehabilitation costs that required admission to the community hospital were also estimated by the total charge. A standardised rate obtained from the pharmacy was used to calculate unit prices for osteoporosis-related prescription medications (Table 5.1). Costs were estimated by multiplying the number of medications prescribed by the unit cost of each medication. Non-prescription medications such as vitamins or supplements are not

eligible for government subsidies and were estimated based on receipts provided by the patient.

Table 5.1: Osteoporosis-related prescription medications

Drug	Brand name
Alendronate	Fosamax 10 mg®
	Fosamax 70 mg®
Denosumab	Prolia 60 mg®
Risedronate	Actonel 35 mg®
Strontium Ranelate	Protelos 2 g®
Teriparatide	Forteo 20 mcg®
Zoledronate	Aclasta 5 mg®
	Zometa 5 mg®
Calcitonin *(nasal spray)*	Calcitonin Novartis Nasal Spray®
Calcium carbonate *(450 mg) + Vit D (200 IU)*	Non-specific
Vitamin D3 *(1,000 / 5,000 IU)*	Lynae®
Ergocalciferol *(1.25 mg) + Vit D (50,000 IU)*	Non-specific

Estimation of direct non-medical costs

Direct non-medical costs consisted of transportation, healthcare and community services as well as special equipment and home/car modifications. Healthcare and community services included but were not limited to massage therapy, acupuncture, traditional Chinese medicine (TCM), meal delivery, domestic helpers and community private nursing. Special equipment and home/car modifications included but were not limited to bathroom equipment (commode, handle bars), bedroom room equipment (rope ladder, mattress), crutches, wheelchairs, home modifications (ramps, steps alteration) and car modifications (seat alteration, steering devices).

Direct non-medical costs are not eligible for government subsidies and were estimated as total charge based on the receipts provided by the patient. Transportation via personal car was calculated based on the distance travelled multiplied by the unit cost of petrol (S$0.45/km) [184]. The use of mass rapid transit (MRT), bus or taxi were estimated using a web-based calculator [185]. The cost for a domestic helper was estimated using a conservative rate of 50% of their total salary per month, with the assumption that the helper would not be spending a 100% of his or her time caring for the patient.

Estimation of indirect costs

Indirect costs were estimated using the human capital approach rather than the friction-cost method because the former is grounded in neoclassical economic theory while the latter is not [186]. Moreover, Singapore's unemployment rate in 2013 remained low, and it is only in the case of labour market imperfections or periods of high unemployment that the friction-cost approach should be considered [61]. Productivity loss due to absence from work and costs of informal (unpaid) care provided by family members and/or other persons were included in the indirect cost estimation. Working patients were asked their current occupation and to estimate how many days and/or hours of productivity had been lost because of their fracture. As individual hourly wage rates were not available, monthly occupational wages obtained from the Ministry of Manpower (MOM) [187] were used to

derive hourly earnings with the assumption that a full-time worker is employed 5 days per week, 8 hours per day. Absenteeism was thus calculated by multiplying the number of hours of absence from work with the hourly rates. The occupation "housekeeper" was used to calculate the hourly earnings of patients who were homemakers. Informal care was estimated using the same method above. Patients were asked the occupation of their primary caregiver and to estimate the hours of care provided by them. For caregivers who were employed, the occupational wages from MOM was used and multiplied by the number of hours spent on caring for the patient. The occupation "housekeeper" was used for caregivers who were homemakers or have retired.

Statistical analysis

Descriptive statistics (frequency, percentage, mean, median, standard deviation and 90th percentile) were used to present costs and patients' demographics. Before-subsidy charges were used for cost estimation when taking the hospital's perspective, which included only direct medical costs, while after-subsidy charges were used for cost estimation when taking the patient's perspective, which included direct medical costs as well as direct non-medical costs and indirect costs. Only osteoporotic fracture-related costs were included. Discounting was not required because all costs estimated were for a 3-month period and were reported in Singapore currency (S$) using year 2013

prices. All statistical analyses were performed using SPSS version 22.0 (SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics

A total of 104 eligible patients were approached: 67 (16 acute; 51 prevalent) agreed to participate in this study, giving a response rate of 64.4%. The socio-demographic profile of the patients is shown in Table 5.2. A majority of patients were female (89.6%), Chinese (88.1%), married (59.7%), non-smokers (95.5%), retired (70.1%), and living with their spouse, children or relatives (92.5%). The mean (±SD) age was 73.7 ± 10.8 years and mean (±SD) duration of fracture was 2.7 ± 2.6 years. Approximately one-third of the patients did not attend school (38.8%) and had a monthly household income between S$1,000 to S$2,999 (34.3%). The number of patients who had a spouse (34.3%) serving as their primary caregivers was similar to the number who had other help such as a domestic helper (35.8%). More than half of the patients declined using private insurance (88.1%) or government programs (77.6%) to file claims for the expenses related to their fracture, and only a handful received money from Medifund (4.5%) and health insurance from their employer (3.0%). The most common fractures identified were those of the vertebral column (43.3%) and hip (34.3%), and 88.1% of patients were experiencing their first fracture.

Table 5.2: Socio-demographic and clinical characteristics of patients with osteoporotic fractures 2013 (n=67)

Characteristic	n (%)* or mean ± standard deviation
Individual level variables	
Age (years)	73.7 ± 10.8
Gender	
Female	60 (89.6)
Male	7 (10.4)
Race	
Chinese	59 (88.1)
Indian	4 (6.0)
Malay	3 (4.5)
Others	1 (1.5)
Marital status	
Married	40 (59.7)
Widow	24 (35.8)
Single	3 (4.5)
Highest level of education	
No school	26 (38.8)
Primary	18 (26.9)
Secondary	14 (20.9)
Junior college / polytechnic	4 (6.0)
University	5 (7.5)
Monthly household income (S$)	
No income	12 (17.9)
<1,000	4 (6.0)
1,000-2,999	23 (34.3)
3,000-4,999	10 (14.9)
>5,000	18 (26.9)
Smoking status	
Non-smoker	64 (95.5)
Smoker	3 (4.5)
Employment status	
Retired	47 (70.1)
Employed	6 (9.0)
Unemployed	1 (1.5)
Other	13 (19.4)
Current living arrangement	
Live with spouse / children / relatives	62 (92.5)
Live alone	2 (3.0)
Other	3 (4.5)
Primary caregiver	
Spouse / partner	23 (34.3)
Daughter / son	20 (29.9)
Other	24 (35.8)
Receive money from Medifund	
No	64 (95.5)
Yes	3 (4.5)
Plan to use government schemes[1]	
No	52 (77.6)
Yes	15 (22.4)
Plan to use private health insurance	
No	59 (88.1)
Yes	8 (11.9)

Table 5.2: Socio-demographic and clinical characteristics of patients with osteoporotic fractures 2013 (n=67) *(continued)*

Characteristic	n (%)* or mean ± standard deviation
Receive health insurance from employer	
No	65 (97.0)
Yes	2 (3.0)
Fracture-related variables	
First fracture	
No	8 (11.9)
Yes	59 (88.1)
Duration of fracture (years)	2.7 ± 2.6)
Fracture type	
Vertebral column (spine)	29 (43.3)
Hip	23 (34.3)
Humerus	6 (9.0)
Wrist	2 (3.0)
Other[2]	7 (10.4)

* Percentages may not add up to 100% due to rounding

[1] Includes Medisave, Medifund, Medishield or Eldershield

[2] Includes patella, elbow, tibia and pelvis

3-month costs of osteoporotic fractures

Taking the hospital's perspective, the mean direct medical cost of osteoporotic fractures was found to be S$3,886.9 (US$1.0 = S$1.3 as of December 2013) [73], of which S$2,884.0 was for inpatient services, S$23.4 for A&E services and S$979.6 for outpatient services (Table 5.3). The main cost driver was inpatient costs (74.2%), while A&E services (0.6%) were only a small portion of the total costs. The major source of costs for outpatient services was rehabilitation services, which accounted for 13.7% of the total cost, or 54.3% of the outpatient cost. Findings were similar from the patient's perspective, with inpatient services (57.9%) being the main cost driver of the total cost and rehabilitation services (53.9%) being the major cost contributor for outpatient services. Overall, the costs from the patient's perspective

were lower than those from the hospital's due to deductions from government subsidies.

The mean 3-month direct and indirect costs were S$11,438.7 (acute) and S$1,015.4 (prevalent), of which 34.7% and 8.0%, respectively, accounted for inpatient services. Healthcare expenditure across all services was substantially higher in acute patients than prevalent patients except for outpatient medications and healthcare and community services. Outpatient services were more utilised in the prevalent arm, which is evident when comparing the proportion of outpatient costs to the total costs. It is noteworthy that a huge disparity for outpatient rehabilitation costs was shown in the acute group, and the same was true for medications in the prevalent group. Furthermore, although the proportion of transport costs and the use of special equipment or home/car modifications were similar in both groups, the mean costs were much higher in the acute group. Indirect costs were also substantially higher in acute patients (Table 5.4).

Table 5.3: Direct medical costs incurred by the hospital and patient at different sites of care (n=67)

Site of care	*Hospital*[1]	*Patient*[2]
Inpatient		
Mean	2,884.0	1,010.2
SD	± 6,650.0	± 2,405.7
Median	0.0	0.0
90th percentile	13,621.1	4,292.3
Percentage of total cost (%)*	74.2	57.9
Accident & Emergency		
Mean	23.4	13.4
SD	± 89.1	± 53.4
Median	0.0	0.0
90th percentile	0.0	0.0
Percentage of total cost (%)*	0.6	0.8
Outpatient		
Mean	979.6	721.6
SD	± 2,656.1	± 2,258.3
Median	344.0	226.1
90th percentile	1,477.2	1,018.9
Percentage of total cost (%)*	25.2	41.3
Outpatient physician visits		
Mean	263.4	138.5
SD	± 288.0	± 152.6
Median	208.1	112.4
90th percentile	533.4	332.3
Percentage of total outpatient cost (%)*	26.9	19.2
Outpatient laboratory tests		
Mean	19.6	10.1
SD	± 117.1	± 62.9
Median	0.0	0.0
90th percentile	0.0	0.0
Percentage of total outpatient cost (%)*	2.0	1.4
Outpatient rehabilitations		
Mean	532.3	389.2
SD	± 2,615.4	± 2,211.4
Median	0.0	0.0
90th percentile	56.7	27.3
Percentage of total outpatient cost (%)*	54.3	53.9
Outpatient medications		
Mean	164.3	149.7
SD	± 267.4	± 241.4
Median	65.9	68.0
90th percentile	774.8	700.0
Percentage of total outpatient cost (%)*	16.8	20.7
TOTAL COST		
Mean	3,886.9	1,745.2
SD	± 8,463.5	± 4,043.9
Median	413.1	265.0
90th percentile	14,258.4	4,670.1

* Percentages may not add up to 100% due to rounding
[1] Before governement subsidy charges
[2] After government subsidy charges

Table 5.4: Direct and indirect costs incurred by the patient according to patient type

		Acute (n=16)	*Prevalent (n=51)*
Direct medical costs	***Inpatient***		
	Length of stay (days)	10.1 ± 7.4	0.3 ± 1.4
	Mean	3,972.3	80.9
	SD	± 3,543.7	± 428.3
	Median	3,684.3	0.0
	90th percentile	9,025.7	0.0
	Percentage of total cost (%)*	34.7	8.0
	Accident & Emergency		
	Mean	38.9	5.4
	SD	± 81.9	± 38.5
	Median	0.0	0.0
	90th percentile	174.0	0.0
	Percentage of total cost (%)*	0.3	0.5
	Outpatient		
	Mean	38.9	5.4
	SD	± 81.9	± 38.5
	Median	0.0	0.0
	90th percentile	174.0	0.0
	Percentage of total cost (%)*	0.3	0.5
	Outpatient physician visits		
	Mean	212.1	115.4
	SD	± 115.1	± 156.5
	Median	194.5	56.2
	90th percentile	387.1	209.2
	Percentage of total outpatient cost (%)*	11.0	30.5

Outpatient laboratory tests		
Mean	31.4	3.4
SD	± 125.6	± 17.5
Median	0.0	0.0
90th percentile	150.7	0.0
Percentage of total outpatient cost (%)*	1.6	0.9
Outpatient rehabilitations		
Mean	1,541.4	27.8
SD	± 4,421.5	± 179.9
Median	0.0	0.0
90th percentile	8,257.4	0.0
Percentage of total outpatient cost (%)*	80.2	7.4
Outpatient medications[1]		
Mean	138.0	231.2
SD	± 236.1	± 414.9
Median	54.7	104.1
90th percentile	503.4	783.4
Percentage of total outpatient cost (%)*	7.2	61.2

Table 5.4: Direct and indirect costs incurred by the patient according to patient type *(continued)*

		Acute (n=16)	*Prevalent (n=51)*
Direct non-medical costs	***Transport***		
	Mean	121.9	28.1
	SD	± 128.1	± 29.4
	Median	74.9	16.5
	90th percentile	367.3	66.4
	Percentage of total cost (%)*	1.1	2.8
	Other healthcare and community services		
	Mean	157.8	372.4
	SD	± 334.1	± 438.4
	Median	0.0	0.0
	90th percentile	850.5	975.0
	Percentage of total cost (%)*	1.4	36.7
	Special equipments and home/car modifications		
	Mean	376.6	19.9
	SD	± 685.6	± 68.3
	Median	67.0	0.0
	90th percentile	1,929.7	54.9
	Percentage of total cost (%)*	3.3	2.0

Table 5.4: Direct and indirect costs incurred by the patient according to patient type *(continued)*

		Acute (n=16)	*Prevalent (n=51)*
Indirect costs	***Absenteeism***		
	Hours of productivity loss	76.7 ± 134.3	1.8 ± 4.5
	Mean	609.8	24.0
	SD	± 1,062.6	± 91.3
	Median	161.0	0.0
	90th percentile	3,069.9	62.6
	Percentage of total cost (%)*	5.3	2.4
	Informal care		
	Hours of informal care	237.5 ± 313.5	4.7 ± 5.2
	Mean	4,238.5	107.0
	SD	± 11,919.0	± 291.8
	Median	858.9	50.0
	90th percentile	18,109.5	232.2
	Percentage of total cost (%)*	37.1	10.5
TOTAL COST			
	Mean	11,438.7	1,015.4
	SD	± 14,320.1	± 1,018.4
	Median	5,721.4	839.0
	90th percentile	37,642.8	1,775.2

* Percentages may not add up to 100% due to rounding

[1] Includes prescription and non-prescription medications

Discussion

This prevalence-based COI study provides the first realistic estimate of the burden of osteoporosis-related fractures occurring both acutely and prevalently in patients in Singapore. The costs reported indicate that these fractures had a substantial financial impact on both the hospital and patients.

The direct medical cost per patient estimated in this present study was S$3,886.9 (hospital perspective), and this appears to be similar to figures reported in other Asian countries. A study in China reported an estimate of approximately CNY$15,736.9 [188] per patient, while in Taiwan it costs NT$100,000.0 for the management of osteoporotic fractures [189]. However, when taking the patient's perspective, the cost per patient estimate was greatly reduced by more than half to S$1,745.2. This is due to the highly subsidised rate of up to 50% for SOC or polyclinic visits provided by the government of Singapore. In addition, Singaporeans were eligible for inpatient subsidies of up to 65% or more depending on the patient's financial status through means-testing [190, 191]. Notably, direct medical costs reported in the American [192, 193] and European continents [194-196] were much higher than those estimated in this study. As the comparisons were based on different study time periods, applying different methodology and/or cost items, in addition to different study time frame among

different populations across several continents, caution is required when interpreting the differences.

Despite the difference in total costs estimated between hospital's and patient's perspectives, inpatient costs remained the main cost contributor, which is consistent with previous osteoporotic-fracture COI studies [192, 193, 197-199]. In terms of outpatient costs, rehabilitation services contributed to the bulk of the total expenditure, which is understandable since rehabilitation admissions were included in this category. Like inpatient admissions, although rehabilitation admissions were also eligible for government subsidies in the 6 or 8-bedded wards [200]; however, the rehabilitation costs were significantly lower than inpatient admissions, perhaps because of lower ward charges and fewer resources used in addition to a shorter LOS. Often, the high cost in inpatient services are strongly correlated to LOS, with a higher LOS resulting in higher costs [121, 122]. Though perhaps not intuitive, the health consequences of shortened hospital stays may in fact be positive, if coupled with adequate rehabilitation services after discharge. One study [201] reported significant cost savings when patients had early discharge from the hospital succeeded by community-based rehabilitation, which allows for faster retraining of physical independence and other activities of daily living. This study suggests that attempts to expedite early discharge from hospital to a community-based rehabilitation setting may be worthwhile in reducing overall costs.

Cost of osteoporosis-related fractures within the first 4 weeks of occurrence is concerning, with healthcare use being significantly higher when compared to prevalent patients. This vast disparity was mainly due to inpatient and outpatient rehabilitation costs that greatly increased the burden for acute cases, which is attributed to longer LOS, multiple diagnostic tests and higher resource consumption [121, 122, 202]. Complications and comorbidities were also more likely to occur within the first few weeks following a fracture, and these results in higher healthcare costs [188, 203, 204].

In contrast, direct non-medical costs were higher in the prevalent group, with healthcare and community services being the greatest generator of costs. The main reason for the difference is that domestic helpers were employed by majority of the prevalent patients whereas caregivers such as family members were the main source of assistance in the acute group. As expected, transport costs and the utilisation of special equipment and home/car modifications were noticeably higher in the acute arm. Due to the acute phase of the fracture, private or public ambulances were mainly used as the main mode of transportation, which were more costly than public transport or personal car. Furthermore, all acute patients had no previous fracture, hence the need for special aids such wheelchairs or walkers, in addition, home modifications such as the installation of ramps and handlebars also played a role in the high costs. This finding indicates a need to implement equipment rental services within the hospital

compound and/or subsidies and programs for home modifications for patients, particularly elderly patients with financial difficulties.

In this study, indirect costs were also examined. When the whole patient sample is considered, the estimated cost of absenteeism was fairly low because few of the patients were below 65 years of age and working. Informal care was the most significant cost contributor when the fracture was recent; a majority of caregivers were the patient's spouse who had mostly retired or the patient's children who had to give up their remunerated work. Contrary to the common opinion that indirect costs far exceed direct costs [20, 103], the findings in this study were less decisive. However, similar findings were reported in two osteoporotic fracture-related COI studies where direct costs were higher than indirect costs [61, 205]. The proper way of estimating and including indirect costs has been subjected to considerable debate [31, 32]; therefore, the higher costs seen in other studies might be due to an overestimation of the true cost or the use of a different methodology than those applied in this study. The present study's cost estimates from the hospital's perspective are noticeably much lower than those obtained by three previous studies done in Singapore [181, 206, 207]. Chen et al [206] estimated an average cost of S$9,347.5, while S$7,367.0 was reported by Wong et al [207] and S$10,515.0 by Lee et al [181]. However, it should be noted that these studies had different study durations and only estimated hospitalisation costs of hip fractures.

Osteoporosis is a silent condition and in the absence of a fragility fracture, it can go undetected for many years. Usually by the time a fracture occurs, the consequences of high healthcare costs are unavoidable. Therefore, prevention of fractures using the 'case-finding' approach should be adopted (i.e. subjects at high risk of fractures should be identified and treated) [208].

This study is not without limitations. First, patients were selected from a single tertiary hospital, which limits the study's external validity. Second, due to the small sample size, regression analysis to determine the predictors of total costs could not be established; therefore, further research in this area is warranted to draw a more definitive conclusion.

Conclusion

This study provides a comprehensive cost analysis for patients with osteoporotic fractures in Singapore. The results indicate that fragility fractures represent a large cost burden to the healthcare system during the first 4 weeks post-fracture. Inpatient hospitalisations were associated with the highest cost borne by both the hospital and patient, and informal care costs dominated indirect costs. This study's follow-up period of three months may seem short for chronic disease cost assessment. Future studies with a longer data collection period or extrapolation using modelling techniques are needed.

With an aging population, the prevalence of osteoporosis-related fractures in Singapore will continue to grow in the years to come, resulting in a heavy burden on health budgets. Better knowledge of the financial consequences of fragility fractures will enable health-system reform to minimise the long-term economic burden of this growing concern.

CHAPTER SIX

Conclusion and Future Studies

Chapter 6 Conclusion and Future Studies

Major Findings

The first study of this thesis examined the methods used in the identified COI studies of DM and found that the studies varied considerably in their study design, perspective and included cost categories. Direct costs were included in the majority of the studies, with hospital inpatient care, physician services and medications serving as the most commonly used cost categories. Furthermore, amongst the reviewed studies, the societal perspective was the most commonly taken. The findings regarding the economic impact of DM reported estimated total annual costs that ranged from US$141.6 million to US$174.0 billion; direct costs ranged from US$150.0 to US$14,060 pppy whereas indirect costs ranged from US$39.6 to US$7,164 pppy. Inpatient cost was the major contributor to direct cost in half of the studies that included inpatient costs, physician services and medications. DM-related excess costs between DM patients and non-DM patients ranged from US$123.1 to US$10,837 pppy with the excess cost ratio ranging from 1.5 to 4.4. The cost ratio for a patient with DM complications to a patient without them ranged from 1.9 to 2.1.

In the second study conducted for this thesis, the total direct medical cost of T2DM was estimated with a mean annual cost of S$2,034.6, of which 60.8% was accounted for by inpatient services, 35.1% by

outpatient services and 4.1% by A&E services. The major source of cost for outpatient services was physician visits, which accounted for 22.6% of the total healthcare expenditure and 64.0% of total outpatient expenditure. Independent determinants of total costs were DM interventions such as the use of insulin only and the combination of oral medications and insulin as well as having cerebrovascular, cardiovascular, peripheral vascular disease and nephropathy complications.

The third study estimated the mean annual direct medical cost of stroke to be S$12,473.7, of which 93.6% was accounted for by inpatient services, 4.9% by outpatient services and 1.5% by A&E services. Healthcare expenditure across all services was substantially higher in acute patients than prevalent patients. The mean annual costs were S$22,721.3 (acute) and S$2,226.2 (prevalent), of which 95.5% and 73.5%, respectively, accounted for inpatient services. Outpatient services were more utilised in the prevalent arm. Independent determinants of greater total costs were stroke types, such as IS, SAH and ICH, shorter post-stroke period, more than one complications and a greater number of comorbidities.

In the final study, the total direct and indirect costs of osteoporotic fractures in Singapore were estimated. The mean annual direct medical cost taking the hospital's perspective was found to be S$3,886.0, of which S$2,884.9 was for inpatient services, S$23.4 for

A&E services and S$979.6 for outpatient services. Of the total healthcare expenditure, the main cost driver was inpatient costs, while A&E services were only a small portion of the total costs. The major source of costs for outpatient services was rehabilitation services, which accounted for 13.7% of the total healthcare expenditure and 54.3% of total outpatient expenditure. Findings were similar from the patient's perspective, with inpatient services being the main cost driver of the total costs while rehabilitation services were the major cost contributor for outpatient services. Overall, the costs from the patient's perspective were much lower due to deductions from government subsidies. Comparing acute and prevalent patients, the mean annual direct and indirect costs were S$11,438.7 (acute) and S$1,015.4 (prevalent). Direct costs were higher than indirect costs, with the bulk of costs incurred by inpatient services. Healthcare expenditure across all services was substantially higher in acute patients than prevalent patients, except for outpatient medications and healthcare and community services.

Major Contributions

This thesis has contributed new information on the economic burden of DM, stroke and osteoporosis-related fractures in Singapore that was previously unavailable. This research not only suggests the need for management of these chronic conditions, but also appropriate healthcare decision-making. First, to the best of our knowledge, this

thesis was the first to describe the methods and summarise the findings reported in published DM COI studies from 2007 to 2011. This led to the finding of the strengths and limitations of the various methods utilised as well as a description of how the application of different methods influenced reported cost estimates. Second, this thesis provided comprehensive and robust information regarding the financial burden of DM, stroke and osteoporotic fractures in Singapore by estimating both direct and indirect costs (osteoporotic fractures) from the hospital's and patient's perspective. Important suggestions were proposed to local decision-makers such as the government, healthcare professionals, policymakers and patients, with the aim of reducing the economic burden by intervention programs or the reallocation of resources to those of higher priority. Third, this thesis revealed the predictors of total costs in both DM and stroke. As such, there is an imperative need for healthcare institutions to review current guidelines on effective discharge planning and develop patient-targeted disease management programs to reduce overall LOS as well as complications and comorbidities.

Major Limitations

The limitations of the studies in this thesis have been discussed in details in the individual chapters and are briefly summarised here. First, data for both DM and stroke patients were drawn from a healthcare database and, as such, relied on the accuracy and completeness of

those records. Second, intangible costs were not examined; hence the true cost of the disease has likely been underestimated. Third, the study population was limited to the public healthcare sector in Singapore. Therefore, the findings may not be generalisable to the entire population.

Future Studies

Based on the findings obtained from the above studies, this thesis raises new research questions that should be addressed in the future.

- Economic evaluations alongside controlled intervention studies are needed to draw definitive conclusions, especially in stroke and osteoporosis patients, in order to determine if the changes in severity of the disease, as assessed by lab-derived measurements would alter the overall cost.
- The predictors of total cost in patients with osteoporotic-fractures could be estimated with a larger sample.
- Studies could incorporate patients with and without the disease (matched-cohort) so that estimated costs can be attributed exclusively to the disease.
- Further pharmacoeconomic evaluations such as cost-effectiveness and cost-utility analysis alongside outcomes research surveys (i.e. health-related quality of life) could be conducted. The results would

provide more holistic information about patients with chronic conditions.

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Appendices

Appendix I Baseline (Acute) Cost of Osteoporotic Fractures Questionnaire

COST OF OSTEOPOROTIC FRACTURE SURVEY
(BASELINE ≤ 4 WEEKS)

Hospital: **SURVEY ID: |__|__|__|**

Thank you for your participation in this questionnaire. This study will provide information about the total cost of osteoporotic fractures and resource utilisation associated with the fracture, which will be used to assist in future healthcare planning.

This study has been approved by the Institutional Review Board/Ethics Committee.

You are asked to fill in a simple **confidential questionnaire** assessing the direct costs (such as expenditures on prescription and over-the-counter medications, services by healthcare providers etc.) and indirect costs (such as the value of work lost) due to your fracture.

If you have any questions or wish for further information about this study please contact

_____.

INTERVIEW DATE: |__|__| / |__|__| / |__|__|__|__|
MONTH DAY YEAR

TIME START: |__|__|:|__|__| AM PM TIME END: |__|__|:|__|__| AM PM

TOTAL TIME TAKEN FOR INTERVIEW: _____MINUTES

SECTION A GENERAL INFORMATION

We would like to obtain your contact number so we can send a text or phone call to remind you about the 3-month follow-up. Please be assured that your contact number will remain confidential. Thank you.

Contact number: _____

*QA1. **When did this fracture occur?**

_____/_____/_____ (day/ month/ year)

*QA2. **Type of fracture:**

1 Vertebral column (spine) 2 Rib 3 Hip 4 Wrist
5 Other

If other, please specify _____

QA3. **Is this your first fracture?**

1 Yes 2 No

If no, please specify the number of previous fractures _____ and the type(s) of fracture _____

QA4. **Are you a citizen or permanent resident of Singapore?**

1 Yes 2 No 3 Don't know

*QA5. **Marital status:**

1 Married 2 Widow 3 Single 4 Divorced

*QA6. **Highest level of education:**

1 No school 2 Primary 3 Secondary 4 ITE
5 Pre-U/JC 6 Polytechnic 7 University

QA7. **Gross household monthly income:**

1 No income 2 Less than $1,000 3 $1,000 - $2,999 4 $3,000 - $4,999
5 $5,000 - $6,999 6 $7,000 or above

QA8. **Do you smoke?**

1 Yes 2 No

*QA9. **What is your <u>current</u> employment status?**

1 Employed (go to QA9.1) 2 Unemployed (go to QA9.2) 3 Retired (go to QA9.3) 4 Other (go to QA9.4)

QA9.1. 1) What is your occupation? _____

2) How many hours do you work per day _____ and days per week _____

3) Since the occurrence of your fracture, how many days <u>have you taken</u> time off from work due to the fracture and/or to attend medical appointments? ____ days

4) Since the occurrence of your fracture, how many days have you had difficulty working at your job due to your fracture? ____ days

5) Please estimate the percent your work capacity that has been reduced due to the fracture ___ %

QA9.2. 1) Unemployed because of:

a) Your fracture b) Other health problems c) Unable to find work

d) Other, please specify _____

QA9.3. 1) What was your occupation at the time you retired? _____

2) Did you retire due to your fracture? Yes/No

3) Do you receive a pension (CPF)? Yes/No

QA9.4. 1) Other, please specify _____

*QA10. **What is your <u>current</u> living arrangement?**

1	Live alone	2	Live with your spouse, children, relatives	3	Live in nursing home	4	Other

If other, please specify _____

*QA11. **Who is your primary caregiver?**

1	Spouse/ Partner	2	Daughter/Son	3	Friend/ Neighbour	4	Other

If other, please specify _____

QA12. **Did your caregiver miss work, leave their job or change jobs because they had to care for you due to your fracture?**

1	Miss work (go to QA12.1)	2	Leave job (go to QA12.2)	3	Change job (go to QA12.3)	4	Other (go to QA12.4)

QA12.1. 1) How many days of missed work since the onset of your fracture? _____ days

2) What is their occupation? _____

3) How many hours of care have you received from your caregiver per week on average since the onset of your fracture? _____ hours

4) Is your caregiver paid for the services they provide to you? Yes/No

If yes, how much S$_____

QA12.2. 1) What was their occupation before leaving the job? _____

2) How many hours worked per day _____ and days per week _____

QA12.3. 1) What was their previous job? _____

2) How many hours worked per day _____ and days per week _____ at the <u>previous</u> job

3) How many hours worked per day _____ and days per week _____ at the <u>new</u> job

QA12.4. 1) Other, please specify _____

QA13. **Do you currently receive money from Medifund?**

1	Yes	2	No	3	Don't know

QA14. **Do you plan to use Medisave, Medishield, Medifund or Eldershield to claim for the expenses related to your fracture?**

1	Yes	2	No	3	Don't know

If yes, please specify Medisave, Medishield, Medifund or Eldershield _____

QA15. **Do you plan to use any private health insurance—this includes any Medisave-approved Integrated Shield plans offered by a private insurer (e.g. NTUC Income's IncomeShield)—to claim for the expenses related to your fracture?**

1	Yes	2	No	3	Don't know

If yes, please specify the name of the insurer _____

QA16. **Do you have any health insurance through your employer?**

1 Yes 2 No 3 Don't know

If yes, please specify name of insurer _____and

Do you plan to use this insurance to claim for the expenses related to your fracture? (Yes/No)

The following sections ask about the use of health services as a result of your fracture. Some of these questions ask for information that may be difficult for you to remember. It would be better if you could provide us with a copy of the bills or receipts for any medical care visits you have had since the occurrence of your fracture, along with the bottles of your prescription medications. If possible, please make those available, as it will greatly reduce the time required to complete this questionnaire.

SECTION B INPATIENT SERVICES

ACUTE CARE HOSPITAL/COMMUNITY HOSPITAL

Have you been hospitalized due to your fracture? These include both government and private hospitals.

1 Yes 2 No (please go to Section C)

If yes, please specify which hospital _____

How many times were you admitted overnight due to your fracture?

Number of admissions: ☐☐

For each of the inpatient admissions you listed, we are going to ask you some additional questions in the table below.

[If QB1 = Yes, complete QB3-QB9 for each admission]

QB3. What was the name of the hospital where **[fracture patient's name]** was admitted?

QB4. What was the date of admission?

QB5. What was the date of discharge?

QB6. What type of transportation did **[fracture patient's name]** use to travel to the hospital — ambulance, taxi, bus, MRT, personal car, walk, or other (please list)?

[1 = Ambulance, 2 = Taxi, 3 = Bus, 4 = MRT, 5 = Personal Car, 6 = Walk, 7 = Other: please specify]

QB7. Did **[fracture patient's name]** pay for this admission using any of the following sources: Medisave, Medishield, Medifund or private insurance? Please list all that apply. **[1 = Medisave, 2 = Medishield 3 = Medifund, 4 = Private insurance, 5 = Other: please specify]**

QB8. What was the total charge **before** government subsidy for the hospital admission (in SGD)?

QB9. What was the total charge **after** government subsidy for the hospital admission (in SGD)?

QB10. Is the total charge based on original receipts? **[1 = Yes, 2 = No]**

[Repeat for each hospital admission]

Responses to questions about inpatient stay

Admission number	QB3. Hospital name	QB4. Date of admission	QB5. Date of discharge	QB6. Mode of transportation **[1 = Ambulance 2 = Taxi 3 = Bus 4 = MRT 5 = Personal Car 6 = Walk 7 = Other: please specify]** Please specify	QB7. Other sources of payment **[1 = Medisave 2 = Medishield 3 = Medifund 4 = Private Insurance 5 = DK* 6 = Other: please specify]**	QB8. Total bill in (S$) before subsidy	QB9. Total bill in (S$) after subsidy	QB10. Is the total charge based on original receipts? **[1 = Yes 2 = No]**
Example	**National University Hospital (NUH)**	**01/01/13**	**03/01/13**	**2; S$13.00**	**2**	**S$350.00**	**S$100.00**	**1**
1								
2								
3								
4								
5								

***DK = Don't know**

SECTION C EMERGENCY DEPARTMENT SERVICES

QCC1. **Have you at any time after your fracture received care in a hospital emergency department that did not result in a hospitalisation (i.e. not admitted directly to the hospital)?**

1 Yes 2 No (go to Section D)

If yes, please specify the **number of times** you received care in the emergency department: ☐☐

For each of the emergency department visits you listed, we are going to ask you some additional questions in the table below.

[If QC1 = Yes, complete QC2-QC12 for each of the listed admissions]

QC2. What was the name of the hospital where **[fracture patient's name]** received emergency department care?

QC3. What type of transportation did **[fracture patient's name]** use to travel to the emergency department — ambulance, taxi, bus, MRT, personal car, walk, or other (please list)? **[1 = Ambulance, 2 = Taxi, 3 = Bus, 4 = MRT, 5 = Personal Car, 6 = Walk, 7 = Other: please specify]**

QC4. What was the duration of the visit? Please list to the nearest hour.

QC5. Who accompanied **[fracture patient's name]** to the hospital?

QC6. Was the visit due to **[fracture patient's name]** fracture? **[1 = Yes, 2 = No, 3 = Don't know]**

QC7. **[If QC6 = No]** Please list the reasons for the visit.

QC8. How much did **[fracture patient's name]** pay out of pocket (in SGD) for this visit?

QC9. Did **[fracture patient's name]** pay for this visit using any of the following sources: Medisave, Medishield, Medifund or private insurance? Please list all that apply. **[1 = Medisave, 2 = Medishield, 3 = Medifund, 4 = Private Insurance, 5 = Don't know, 6 = Other: please specify]**

QC10. What was the total charge **before** government subsidy for the hospital visit (in SGD)?

QC11. What was the total charge **after** government subsidy for the hospital visit (in SGD)?

QC12. Is the total charge based on original receipts? **[1 = Yes, 2 = No]**

[Repeat for each emergency department visit]

Responses to questions about emergency department visits

Visit number	QC2. Hospital name	QC3. Mode of transportation **[1 = Ambulance 2 = Taxi 3 = Bus 4 = MRT 5 = Personal Car 6 = Walk 7 = Other: please specify]** Please specify	QC4. Duration of the visit	QC5. Accompanied by	QC6. Was the visit due to your fracture **[1 = Yes 2 = No** (go to QC7) **3 = DK*]**	QC7. List reasons why you were visiting
Example	**National University Hospital (NUH)**	**2; S$13.00**	**2 hours**	**Wife**	**2**	**Cardiac arrest**
1						
2						
3						
4						
5						

***DK = Don't know**

Responses to questions about emergency department visits (cont'd)

QC8. (S$) value paid out of pocket	QC9. Other sources of payment **[1 = Medisave** **2 = Medishield** **3 = Medifund** **4 = Private Insurance** **5 = DK*** **6 = Other: please specify]**	QC10. Total bill in (S$) before subsidy	QC11. Total bill in (S$) after subsidy	QC12. Is the total charge based on original receipts? **[1 = Yes** **2 = No]**
S$100.00	**1**	**$$350.00**	**S$100.00**	**1**

***DK = Don't know**

SECTION D OUTPATIENT SERVICES

HOSPITAL OUTPATIENT

QD1. **Have you at any time after your fracture received medical care at a hospital outpatient clinic?** These may include any visits for treatment, surgery, health screenings, check-ups, physiotherapy, occupational therapy, or any other type of care received at a hospital outpatient clinic.

1 Yes 2 No (please go to QD15)

If yes, please specify the **number of times** you visited a hospital outpatient clinic: ☐☐

For each of the outpatient hospital visits you listed, we are going to ask you some additional questions in the table below.

[If QD1 = Yes, complete QD2-QD14 for each of the listed visits]

QD2. What was the name of the hospital where **[fracture patient's name]** received care?

QD3. What was the name of the department or specialty where **[fracture patient's name]** received care?

QD4. Was this a private facility or a public facility?

[1 = Private facility, 2 = Public facility, 3 = Don't know]

QD5. What type of transportation did **[fracture patient's name]** use to travel to the clinic — taxi, bus, MRT, personal car, walk, or other (please list)?

QEB1. **[1 = Taxi, 2 = Bus, 3 = MRT, 4 = Personal Car, 5 = Walk, 6 = Other: please specify]**

QD6. What was the duration of the visit? Please list to the nearest hour.

QD7. Who accompanied **[fracture patient's name]** to the hospital?

QD8. Was the visit due to **[fracture patient's name]** fracture? **[1 = Yes, 2 = No, 3 = Don't know]**

QD9. **[If QD8 = No]** Please list the reasons for visit.

QD10. How much did **[fracture patient's name]** pay out of pocket (in SGD) for this visit?

QD11. Did **[fracture patient's name]** pay for this admission using any of the following sources: Medisave, Medishield, Medifund or private insurance? Please list all that apply. **[1 = Medisave, 2 = Medishield, 3 = Medifund, 4 = Private Insurance, 5 = Don't know, 6 = Other: please specify]**

QD12. What was the total charge **before** government subsidy for the outpatient visit (in SGD)?

QD13. What was the total charge **after** government subsidy for the outpatient visit (in SGD)?

QD14. Is the total charge based on original receipts? **[1 = Yes, 2 = No] [Repeat for each visit]**

Responses to questions about hospital outpatient visits

Visit number	QD2. Hospital name	QD3. Department/ Specialty name	QD4. Private or public [**1 = Private facility 2 = Public facility 3 = DK*]**	QD5. Mode of transportation **[1 = Taxi 2 = Bus 3 = MRT 4 = Personal Car 5 = Walk 6 = Other: please specify]** Please specify	QD6. Duration of the visit	QD7. Accompanied by
Example	**National University Hospital (NUH)**	**Physiotherapy**	**2**	**1; S$13.00**	**2 hours**	**Wife**
1						
2						
3						
4						
5						

***DK = Don't know**

Responses to questions about hospital outpatient visits (cont'd)

Visit number	QD8. Were you visiting due to your fracture? **[1 = Yes 2 = No** (go to QD9) **3 = DK*]**	QD9. List reasons why you were visiting	QD10. (S$) Value paid out of pocket	QD11. Other sources of payment **[1 = Medisave 2 = Medishield 3 = Medifund 4 = Private Insurance 5 = DK* 6 = Other: please specify]**	QD12. Total bill in (S$) before subsidy	QD13. Total bill in (S$) after subsidy	QD14. Is the total charge based on original receipts? **[1 = Yes, 2 = No]**
Example	**1**	**Muscle strengthening related to fracture**	**S$100.00**	**1**	**S$350.00**	**S$100.00**	**1**
1							
2							
3							
4							
5							

***DK = Don't know**

LABORATORY TESTS

QD15. **Have you at any time after your fracture undergone laboratory tests at a hospital outpatient clinic?** These may include undergoing any tests such as full blood count, renal function tests, x-ray, CAT scan, MRI, bone mineral density scan etc.

1 Yes 2 No (please go to QD29)

If yes, please specify the **number of tests** you have undergone at a hospital outpatient ☐☐ clinic:

For each of the tests you listed, we are going to ask you some additional questions in the table below.

[If QD15 = Yes, complete QD16-QD28 for each of the listed visits]

QD16. What was the name of the hospital where **[fracture patient's name]** received care?

QD17. What was the name of the department or specialty where **[fracture patient's name]** received care?

QD18. Was this a private facility or a public facility?

[1 = Private facility, 2 = Public facility, 3 = Don't know]

QD19. What type of tests did [fracture patient's name] undergo?

QD20. What type of transportation did **[fracture patient's name]** use to travel to the clinic—taxi, bus, MRT, personal car, walk, or other (please list)?

QEB2. **[1 = Taxi, 2 = Bus, 3 = MRT, 4 = Personal Car, 5 = Walk, 6 = Other: please specify]**

QD21. What was the duration of the visit? Please list to the nearest hour.

QD22. Who accompanied **[fracture patient's name]** to the hospital?

QD23. Was the visit due to **[fracture patient's name]** fracture? **[1 = Yes, 2 = No, 3 = Don't know]**

QD24. How much did **[fracture patient's name]** pay out of pocket (in SGD) for this visit?

QD25. Did **[fracture patient's name]** pay for this admission using any of the following sources: Medisave, Medishield, Medifund or private insurance? Please list all that apply. **[1 = Medisave, 2 = Medishield, 3 = Medifund, 4 = Private Insurance, 5 = Don't know, 6 = Other: please specify]**

QD26. What was the total charge **before** government subsidy for the hospital labs (in SGD)?

QD27. What was the total charge **after** government subsidy for the hospital labs (in SGD)?

QD28. Is the total charge based on original receipts? **[1 = Yes, 2 = No] [Repeat for each visit]**

Responses to questions about hospital outpatient laboratory tests

Test number	QD16. Hospital name	QD17. Department/ Specialty name	QD18. Private or public [**1 = Private facility 2 = Public facility 3 = DK*]**	QD19. Type of test	QD20. Mode of transportation **[1 = Taxi 2 = Bus 3 = MRT 4 = Personal Car 5 = Walk 6 = Other: please specify]** Please specify	QD21. Duration of the visit
Example	**National University Hospital (NUH)**	**Orthopaedic**	**2**	**Bone mineral density scan**	**1; S$13.00**	**2 hours**
1						
2						
3						
4						
5						

***DK = Don't know**

Responses to questions about hospital outpatient laboratory tests (cont'd)

Test number	QD22. Accompanied by	QD23. Were you receiving tests because of your fracture? **[1 = Yes 2 = No 3 = DK*]**	QD24. (S$) Value paid out of pocket	QD25. Other sources of payment **[1 = Medisave 2 = Medishield 3 = Medifund 4 = Private Insurance 5 = DK* 6 = Other: please specify]**	QD26. Total bill in (S$) before subsidy	QD27. Total bill in (S$) after subsidy	QD28. Is the total charge based on original receipts? **[1 = Yes, 2 = No]**
Example	**Wife**	**1**	**S$100.00**	**1**	**S$350.00**	**S$100.00**	**1**
1							
2							
3							
4							
5							

***DK = Don't know**

PRIMARY CARE CLINICS

QD29. **Have you at any time after your fracture received medical care at a primary care clinic?** These may include any visits at government polyclinics or private general practitioners or any other type of care received at a primary care clinic.

1 Yes 2 No (please go to Section E)

If yes, please specify the **number of times** you visited a primary care clinic: ☐☐

For each of the outpatient primary care clinic visits you listed, we are going to ask you some additional questions in the table below.

[If QD29 = Yes, complete QD30-QD41 for each of the listed visits.]

QD30. What was the name of the clinic where **[fracture patient's name]** received care?

QD31. Was this a private facility or a public facility?

[1 = Private facility, 2 = Public facility, 3 = Don't know]

QD32. What type of transportation did **[fracture patient's name]** use to travel to the clinic — taxi, bus, MRT, personal car, walk, or other (please list)?

QEB3. **[1 = Taxi, 2 = Bus, 3 = MRT, 4 = Personal Car, 5 = Walk, 6 = Other: please specify]**

QD33. What was the duration of the visit? Please list to the nearest hour.

QD34. Who accompanied **[fracture patient's name]** to the primary care clinic?

QD35. Was the visit due to **[fracture patient's name]** fracture? **[1 = Yes, 2 = No, 3 = Don't know]**

QD36. **[If QD35 = No]** Please list the reasons for visit.

QD37. How much did **[fracture patient's name]** pay out of pocket (in SGD) for this visit?

QD38. Did **[fracture patient's name]** pay for this visit using any of the following sources: Medifund，private insurance, Chronic Disease Management Programme (CDMP) or Primary Care Partnership Scheme (PCPS)? Please list all that apply. **[1 = Medifund, 2 = Private Insurance, 3 = Chronic Disease Management Programme (CDMP), 4 = Primary Care Partnership Scheme (PCPS), 5 = Other: please specify]**

QD39. What was the total charge **before** government subsidy for the primary care visit (in SGD)?

QD40. What was the total charge **after** government subsidy for the primary care visit (in SGD)?

QD41. Is the total charge based on original receipts? **[1 = Yes, 2 = No] [Repeat for each visit]**

Responses to questions about primary care clinic visits

Visit number	QD30. Clinic name	QD31. Private or public **[1 = Private 2 = Public 3 = DK*]**	QD32. Mode of transportation **[1 =Taxi 2 = Bus 3 = MRT 4 = Personal Car 5 = Walk 6 = Other: please specify]** Please specify	QD33. Duration of the visit	QD34. Accompanied by	QD35. Were you visiting due to your fracture? **[1 = Yes 2 = No 3 = DK*]**	QD36. List reasons why you were visiting
Example	**Alexandra family clinic**	**1**	**1; $13.00**	**2 hours**	**Wife**	**2**	**Fever**
1							
2							
3							
4							
5							

***DK = Don't know**

Responses to questions about primary care clinic visits (cont'd)

Visit number	QD37. (S$) Value paid out of pocket	QD38. Other sources of payment **[1 =Medifund 2 = Private Insurance 3 = CDMP (chronic disease management program) 4 = PCPS (primary care partnership scheme) 5 = Other: please specify]**	QD39. Total bill in (S$) before subsidy	QD40. Total bill in (S$) after subsidy	QD41. Is the total charge based on original receipts? **[1 = Yes, 2 = No]**
1	**S$100.00**	**1**	**S$350.00**	**S$100.00**	**1**
2					
3					
4					
5					

SECTION E REHABILITATION

QE1. **Have you at any time after your fracture received rehabilitation?** These may include any rehabilitation at home, day rehabilitation centers and nursing homes.

1 Yes 2 No (please go to Section F)

If yes, please specify the **number of times** you had rehabilitation sessions: ☐☐

We are going to ask you some additional questions about your rehabilitation sessions in the table below.

[If QE1 = Yes, complete QE2-QE12 for each rehabilitation service]

QE2. What was the name of the agency that provided **[fracture patient's name]'s** rehabilitation care?

QE3. What was the type of rehabilitation centre? **[1 = Home rehabilitation, 2 = Day rehabilitation, 3 = Nursing home rehabilitation, 4 = Other: please specify]**

QE4. Was this a private or public rehabilitation agency? **[1 = Private rehabilitation agency, 2 = Public, 3 = Don't know]**

QE5. What type of transportation did **[fracture patient's name]** use to travel to the clinic — taxi, bus, MRT, personal car, walk, or other (please list)?

QEB4. **[1 = Taxi, 2 = Bus, 3 = MRT, 4 = Personal Car, 5 = Walk, 6 = Other: please specify]**

QE6. On average, how many rehabilitation sessions did **[fracture patient's name]** have per month?

QE7. On average, how long was one rehabilitation session in minutes?

QE8. On average, how much did **[fracture patient's name]** pay out of pocket (in SGD) for one rehabilitation session?

QE9. Did **[fracture patient's name]** pay for these sessions using any other sources? Please list all that apply. **[1 = Medisave, 2 = Medishield, 3 = Medifund, 4 = Private Insurance, 5 = Don't know, 6 = Other: please specify]**

QE10. What was the total charge **before** government subsidy for the rehabilitation services (in SGD)?

QE11. What was the total charge **after** government subsidy for the rehabilitation services (in SGD)?

QE12. Is the total charge based on original receipts? **[1 = Yes, 2 = No]**

Responses to questions about rehabilitation sessions

QE2. Name of agency/nursing home	**Example All Saints Day Rehabilitation Centre**	
QE3. Type of rehabilitation centre **[1 = Home rehabilitation 2 = Day rehabilitation 3 = Nursing home rehabilitation 4 = Other: please specify]**	**2**	
QE4. Private or public **[1 = Private rehabilitation agency 2 = Public rehabilitation agency 3 = DK*]**	**2**	
QE5. Mode of transportation (only applicable to day and nursing home rehabilitation) **[1 = Taxi 2 = Bus 3 = MRT 4 = Personal Car 5 = Walk 6 = Other: please specify]** } Please specify costs	**1**	
QE6. Average number of sessions per month	**1**	
QE7. Average duration of each session in minutes	**2 hours**	
QE8. (S$) Value paid out of pocket per session	**S$50.00**	
QE9. Other sources of payment **[1 = Medisave 2 = Medishield 3 = Medifund 4 = Private Insurance 5 = DK* 6 = Other: please specify]**	**1**	
QE10. Total bill in (S$) before subsidy per session	**S$350.00**	
QE11. Total bill in (S$) after subsidy per session	**S$100.00**	
QE12. Is the total charge based on original receipts? **[1 = Yes, 2 = No]**	**1**	

***DK = Don't know**

SECTION F MEDICATIONS

PRESCRIPTION MEDICATIONS

Have you taken any prescribed medicine after fracture? These include medications that CANNOT be bought over-the-counter and needs a doctor's prescription.

1 Yes 2 No (go to QF8.)

We are going to ask you some additional questions about each of the medication you have TAKEN after fracture.

[If QF1 = Yes, complete QF2-QF7 for each medication]

QF2. What was the name of the prescribed medication?

QF3. How many days did **[fracture patient's name]** take the medication since fracture onset?

QF4. How many times has **[fracture patient's name]** taken the medication per day?

QF5. What was the medication for?

QF6. On average, how much did the medication cost per day?

QF7. Is the total charge based on original receipts? **[1 = Yes, 2 = No]**

Responses to questions about prescribed medications taken in the past 4 weeks

QF2. Name of medication	QF3. Number of days taken since fracture onset	QF4. Times taken per day	QF5. What was the medication for?	QF6. Cost per day (S$)	QF7. Is the total charge based on original receipts? **[1 = Yes, 2 = No]**
Example: Vicodin	**5**	**2**	**Pain relief**	**S$1.00**	**1**

NON-PRESCRIPTION MEDICATIONS

QF8. **Have you taken any non-prescribed medicine/health supplement after fracture?** These include only medications that CAN be bought over-the-counter and do not need a doctor's prescription.

1 Yes 2 No (go to Section G)

We are going to ask you some additional questions about each of the medication/health supplement you have TAKEN after fracture. These may include calcium tablets, vitamins, fish oil, ginseng, Tiger balm, Panadol etc.

[If QF8 = Yes, complete QF9-QF14 for each medication]

QF9. What was the name of the non-prescribed medication?

QF10. How many days has **[fracture patient's name]** taken the medication since fracture onset?

QF11. How many times did **[fracture patient's name]** take the medication per day?

QF12. What was the medication for?

QF13. On average, how much did the medication cost per day?

QF14. Is the total charge based on original receipts? **[1 = Yes, 2 = No]**

Responses to questions about non-prescribed medications/supplements taken in the past 4 weeks

QF9. Name of medication/ supplement	QF10. Number of days taken since fracture onset	QF11. Times taken per day	QF12. What was the medication for?	QF13. Cost per day (S$)	QF14. Is the total charge based on original receipts? **[1 = Yes, 2 = No]**
Example: Fish oil	**2**	**1**	**Strengthen bones**	**S$1.00**	**2**

SECTION G OTHER HEALTHCARE AND COMMUNITY SERVICES

We are now going to ask you about the use of other forms of health services after fracture.

[For each health service listed in the table below, complete QG1-QG4]

QG1. How many times did **[fracture patient's name]** receive this treatment after fracture onset?

QG2. **[If QG1 > 0]** What medical condition or conditions motivated **[fracture patient's name]** to seek this treatment?

QG3. **[If QG1 > 0]** What was the average cost per treatment?

QG4. Is the total charge based on original receipts? **[1 = Yes, 2 = No]**

[Repeat for each health service]

Responses to questions about use of other health services

	Treatment	QG1. Number of times you received this treatment since fracture onset	QG2. Reason for treatment	QG3. Average cost per treatment (S$)	QG4. Is the total charge based on original receipts? **[1 = Yes, 2 = No]**
1	Massage therapy				
2	Acupuncture				
3	Traditional Chinese Medicine (TCM) tui na/bone setting				
4	Homeopathic treatment				
5	Spiritual healing or prayer				
6	Naturopath/ osteopath				
7	Training or practice of meditation, imagery, or relaxation techniques				
8	Other treatment, please specify: _____				

We are now going to ask you about the use of other forms of community services after the fracture.

[For each community services listed in the table below, complete QG5-QG8]

QG5. How many times did **[fracture patient's name]** receive this service after the fracture?

QG6. **[If QG5 > 0]** What was the reason **[fracture patient's name]** requested this service?

QG7. **[If QG5 > 0]** What was the average cost per service?

QG8. Is the total charge based on original receipts? **[1 = Yes, 2 = No]**

[Repeat for each health service]

Responses to questions about use of community services

	Service	QG5. Number of times you received this treatment since fracture onset	QG6. Reason for service	QG7. Average cost per treatment (S$)	QG8. Is the total charge based on original receipts? **[1 = Yes, 2 = No]**
1	Meals delivery				
2	Home cleaning services				
3	Personal helper				
4	Community volunteer help				
5	Community or private nursing				
6	Community transport				
7	Other service, please specify: _____				

SECTION H SPECIAL EQUIPMENT AND HOME/CAR MODIFICATION

We are now going to ask you about the use of special medical equipment or any home/car modifications added as a result of the fracture.

[For each type of medical equipment list in the table below, complete QH1-QH5]

QH1. Did **[fracture patient's name]** use this equipment after fracture?

QH2. Was this equipment purchased or rented by **[fracture patient's name],** or donated by others?

QH3. What was the cost of purchasing or renting this equipment (SGD)? If rented, please give the rental rate in terms of cost per hour, day, week, or month.

QH4. How did **[fracture patient's name]** pay for this purchase – out-of-pocket, private insurance or other (please specify)? **[1 = Out-of-pocket, 2 = Private Insurance, 3 = Don't know, 4 = Other: please specify]**

QH5. Is the total charge based on original receipts? **[1 = Yes, 2 = No]**

[Repeat for each type of equipment]

Responses to questions about use of special equipment and home/car modification

Item number	Special equipment	QH1. Did you use this equipment since fracture onset? **[1 = Yes, 2 = No**]	QH2. Purchased or rented or donated? **[1 = purchased, 2 = rented, 3 = donated]**	QH3. Cost in (S$)	QH4. Source of Payment **[1 = Out-of-pocket, 2 = Private Insurance, 3 = DK*, 4 = Other: please specify]**	QH5. Is the total charge based on original receipts? **[1 = Yes, 2 = No]**
Bathroom equipment						
1	Shower chair/stool					
2	Toilet surround or raised toilet seat					
3	Commode					
4	Hand-held shower					
5	Long-handled brush					
6	Bath board/seat					
7	Other, please specify _____					
Bedroom equipment						
8	Bed blocks to build up bed					
9	Rope ladder for getting out of bed					

10	Other, please specify _____					
Clothing						
11	Sock gutter					
12	Shoehorn/spooner					
13	Velcro replacements					
14	Elastic shoelaces					
15	Special shoes					
16	Inner soles/ orthotics					
17	Other, please specify _____					
Other equipment						
18	Crutches					
19	Canes/walking stick					
20	Quad stick					
21	Walking frame					
22	Walkers					
23	Wheelchair or scooter					
24	Electric lift chair/ smokey dawson chair					
25	Day/night/work splint					
26	Communication equipment, e.g. communication board, speech synthesizer					

27	Other special equipment: _____					
Home modification						
28	Ramps					
29	Steps alteration					
30	Other, please specify _____					
Car modification						
31	Seat alteration					
32	Pedal alteration					
33	Steering devices (e.g. knobs, cuffs etc.)					
34	Other, please specify _____					

***DK = Don't know**

You have reached the end of the questionnaire.
Thank you for your participation.

COST OF OSTEOPOROTIC FRACTURE SURVEY
(BASELINE > 1 YEAR)

Hospital: **SURVEY ID: |__|__|__|**

Thank you for your participation in this questionnaire. This study will provide information about the total cost of osteoporotic fractures and resource utilisation associated with the fracture, which will be used to assist in future healthcare planning.

This study has been approved by the Institutional Review Board/Ethics Committee.

You are asked to fill in a simple **confidential questionnaire** assessing the direct costs (such as expenditures on prescription and over-the-counter medications, services by healthcare providers etc.) and indirect costs (such as the value of work lost) due to your fracture.

If you have any questions or wish for further information about this study please contact _____.

INTERVIEW DATE: |__|__| / |__|__| / |__|__|__|__|
MONTH DAY YEAR

TIME START: |__|__|:|__|__| AM PM TIME END: |__|__|:|__|__| AM PM

TOTAL TIME TAKEN FOR INTERVIEW: _____MINUTES

SECTION A GENERAL INFORMATION

We would like to obtain your contact number so we can send a text or phone call to remind you about the 3-month follow-up. Please be assured that your contact number will remain confidential. Thank you.

Contact number: _____

*QA1. **When did this fracture occur?**

_____/_____/_____ (day/ month/ year)

*QA2. **Type of fracture:**

1 Vertebral column (spine) 2 Rib 3 Hip 4 Wrist
5 Other

If other, please specify _____

QA3. **Is this your first fracture?**

1 Yes 2 No

If no, please specify the number of previous fractures _____ and the type(s) of fracture _____

QA4. **Are you a citizen or permanent resident of Singapore?**

1 Yes 2 No 3 Don't know

*QA5. **Marital status:**

1 Married 2 Widow 3 Single 4 Divorced

*QA6. **Highest level of education:**

1 No school 2 Primary 3 Secondary 4 ITE
5 Pre-U/JC 6 Polytechnic 7 University

QA7. **Gross household monthly income:**

1 No income 2 Less than $1,000 3 $1,000 - $2,999 4 $3,000 - $4,999
5 $5,000 - $6,999 6 $7,000 or above

QA8. **Do you smoke?**

1 Yes 2 No

*QA9. **What is your <u>current</u> employment status?**

1 Employed (go to QA9.1) 2 Unemployed (go to QA9.2) 3 Retired (go to QA9.3) 4 Other (go to QA9.4)

QA9.1. 1) What is your occupation? _____

2) How many hours do you work per day _____ and days per week _____

3) Since the occurrence of your fracture, how many days <u>have you taken</u> time off from work due to the fracture and/or to attend medical appointments? ____ days

4) Since the occurrence of your fracture, how many days have you had difficulty working at your job due to your fracture? ____ days

5) Please estimate the percent your work capacity that has been reduced due to the fracture ___ %

QA9.2. 1) Unemployed because of:

a) Your fracture b) Other health problems c) Unable to find work

d) Other, please specify _____

QA9.3. 1) What was your occupation at the time you retired? _____

2) Did you retire due to your fracture? Yes/No

3) Do you receive a pension (CPF)? Yes/No

QA9.4. 1) Other, please specify _____

*QA10. **What is your <u>current</u> living arrangement?**

1	Live alone	2	Live with your spouse, children, relatives	3	Live in nursing home	4	Other

If other, please specify _____

*QA11. **Who is your primary caregiver?**

1	Spouse/ Partner	2	Daughter/Son	3	Friend/ Neighbour	4	Other

If other, please specify _____

QA12. **Do you currently receive money from Medifund?**

1	Yes	2	No	3	Don't know

QA13. **Do you plan to use Medisave, Medishield, Medifund or Eldershield to claim for the expenses related to your fracture?**

1	Yes	2	No	3	Don't know

If yes, please specify Medisave, Medishield, Medifund or Eldershield _____

QA15. **Do you plan to use any private health insurance—this includes any Medisave-approved Integrated Shield plans offered by a private insurer (e.g. NTUC Income's IncomeShield)—to claim for the expenses related to your fracture?**

1	Yes	2	No	3	Don't know

If yes, please specify the name of the insurer _____

QA16. **Do you have any health insurance through your employer?**

1	Yes	2	No	3	Don't know

If yes, please specify name of insurer _____and

Do you plan to use this insurance to claim for the expenses related to your fracture? (Yes/No)

You have reached the end of the questionnaire.
Thank you for your participation.