Performances of Comorbidity Measures in Healthcare related

Behaviors and Outcomes in Type 2 Diabetes

By

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Dedication

Dedicated to my parents, my sister and my brothers

Acknowledgments

Pursuing this doctoral degree would not be successful without endless support, encouragement, patience, and guidance from a number of individuals in my life. I am deeply indebted to all those people because of whom my graduate adventure has been one that I will cherish forever.

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List of Abbreviations

US United States

DM Diabetes Mellitus

CCI Charlson Comorbidity Index

EI Elixhauser index

CDS Chronic Disease Score

HRQL index Health related Quality of Life index

CIRS Cumulative Illness Rating Scale

ICED Index of Co-existent Disease

HbA1c Glycosylated hemoglobin

UKPSDS United Kingdom Prospective Diabetes Study

OAD medication Oral antidiabetic medication

SUs Sulfonylurea

MET Metformin

TZDs Thiazolidinediones

NHANES National health and Nutrition Examination Survey

MEPS Medical Expenditure Panel Survey

HEDIS Healthcare Effectiveness Data and Information Set

MPR Medication Possession Ratio

ICD-9-CM International Classification of Diseases, 9th revision, Clinical Modification

NDC National Drug Code

ADA American Diabetes Association

HEDIS Healthcare Effectiveness Data and Information Set

NCQA National Committee for Quality Assurance

Chapter
1. Introduction
1.1 Statement of the Problem

With technological advances and improvements in medical care and policy, an increasingly number of patients survives medical conditions that used to be fatal. As a result of this phenomenon, and parallel to the aging of the population, a growing proportion of patients present with multiple coexisting medical conditions. It has been shown that 57 million Americans had multiple chronic conditions in 2000 and that this number will rise to 81 million by 2020 [1], with a consistent trend worldwide [2-6].

The term of "comorbidity" refers to any distinct additional entity that has existed or may occur during the clinical course of a patient who has the index disease under study [7]. The role of comorbidities in the health care system has been an intense area of investigation, due to the awareness of their impact on many facets of health care [8-15]. Outcome measures that have been related to comorbidity include clinical outcomes (i.e., mortality, functional status), health services utilization (i.e., length of hospital stay, number of physician visits, and health care costs) and health related quality of life (HRQOL).

However, measuring comorbidity is not straight forward and a variety of approaches have been used. Depending on the source of data used to develop them, these indexes can be broadly classified into four categories of measures [16]: (1) administrative/claims data based measures (the Deyo adaptation of the Charlson Comorbidity index (CCI) [17]), (2) medical record based measures (e.g., the Cumulative Illness Rating Scale [9] and Kaplan-Feinstein index [11]), (3) self-reported based measures (the Comorbidity Symptom Scale [18]), and (4) clinical judgment based measures (e.g., the American Society of Anesthesiologists Index [19]). Among these measures, the CCI is most widely used, in part, because it has

been widely adapted for users of medical records [20], administrative data [17, 21-28] and patient self-reported data [15, 29]

There has been growing interest in the use of administrative databases for comorbidity assessment, since large databases are increasingly available in many healthcare systems. The main advantages to this approach are ease of data acquisition, cost and time efficiency, particularly given very large study population, and lack of reliance on accurate reporting by patients. Moreover, administrative data can readily assess real-world inpatient and outpatient diagnoses, healthcare utilization experience, and medication use. There are also limitations, such as diagnosis coding errors and omissions [30, 31]. However, administrative databases are an important source of data that can efficiently capture comorbidity among large patient populations.

It has been emphasized that the predictive performance of claims-based comorbidity scores depends on several factors: (1) the clinical conditions included in a comorbidity score and their relative weights, which attempt to account for differential impact of individual comorbidities; (2) the endpoints of study interest (e.g., mortality, healthcare utilization and expenditures); (3) the distribution of comorbid conditions in the source population, which could depend on target study population (e.g., higher prevalence of comorbidities in the elderly, compared to the younger); and (4) the accuracy of the administrative data. [32] The predictive performance of two comorbidity scores can validly be compared when factors 2-4 are held constant. Several studies have explored the predictive validity of comorbidity measures in claims data. However, only a few publications compared the performance o two comorbidity scores in the same populations and for the sample endpoints.

Three types of comorbidity measures have been commonly applied in administrative data based research, They vary in the type of claims sources, including: (1) inpatient claims based comorbidity measures (e.g. the CCI [17] and Elixhauser index (EI) [33]), (2) outpatient claims based comorbidity measures (e.g., Ambulatory Patient Groups (APG) [34]), and (4) pharmacy claims based comorbidity measures (e.g., Chronic Disease Score (CDS)[35]). In addition,

regarding the content of comorbid conditions, these measures can be classified into two types: the *International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM)*-based measures, such as the CCI and EI, and pharmacy claims measures such as the CDS.

Among existing comorbidity measures, the CCI is the most common index used to control comorbidity in the health outcome studies. The CCI was initially developed for use with medical records and consisted of 19 different diseases weighted according the relative risk of death, ranging from 1 to 6. The index has since been adapted into 17-item weighted indexes for use with administrative data. The EI [33]included more exhaustive ICD-9-CM definitions than the Charlson/Deyo method [17] (30 rather than just 17). Recent studies showed that, although both the CCI and EI are valid prediction tool for assessing death [36], but the EI slightly outperformed the CCI in predicting mortality [37, 38].

Moreover, when these diagnosis-based comorbidity measures, such as the CCI, were compared to medication-based indices, such as the CDS, in predicting healthcare utilization, the CCI had better performance in predicting emergency room visits and (non-emergency) hospitalizations, while the CDS had better performance in predicting physician visits and healthcare expenditures [32, 39]. These results demonstrated that the predictive performance of these claim-based comorbidity measures varied in the outcomes of study interest and implied that the effect of comorbidity vary in the types of health related outcomes of interest. The effect of comorbidity on expenditure outcomes is different than the effect of comorbidity when applied to mortality and morbidity outcomes. Previous research findings on the enhanced performance of the CDS scores compared with the CCI and EI may have resulted in part from a difference in the types of utilization of healthcare services. So, we are aware of a research need to examine relative predictive performance of individual comorbidity index across different healthcare related outcomes and further to compare individual index performance with other indexes' for a given outcome of interest. Such a comparison study will be helpful to understand differential impact of comorbidities on healthcare related outcomes and to suggest a comorbidity measure with the best predictive performance when

studying a specific healthcare related outcome. However, a few studies has been conducted to assess differential influence of comorbidities in the healthcare related outcomes comprehensively and to explore and suggest an appropriate comorbidity measure, in terms of predictive ability, when studying a particular healthcare related outcome of interest.

Furthermore, in order to account for differential the impact of comorbidities, some comorbidity indices with a weighting scheme (e.g., the CCI) weight the contributions of different comorbid conditions, depending on their role in the analytic relationship with the outcome of interest. The weights can be directly taken from original index or specifically developed from study own population, which is commonly called study population specific weights. Although assigned integer weights in the original index are relatively practical for clinical use, recent studies show that the predictive performance of comorbidity index was enhanced when study population specific weights were applied, instead of originally assigned weights, raising questions as to what weighting scheme to use [26, 40]. Study population specific weights are the weights empirically derived based on study own population using the approach of developing weighting scheme that was used by original study Further works on the comparison of two weighting scheme based indices is in need and other potential way to generate weighting scheme should be explored further.

The Health Related Quality of Life comorbidity index (HRQL-CI) was recently developed by Mukherjee et al (2009) [41], based on the Medical Expenditure Panel Survey (MEPS) dataset. The development of the HRQL-CI originally attempted to predict the HRQL as main outcome of interest and therefore, it consists of two sub parts: physical and mental health aspects of indexes. Because the disease conditions included in the HRQL-CI are disease diagnosis-based, it can be applied in the claims-based dataset and its predictive performance can be comparable to the CCI's or other disease diagnosis-based comorbidity measures'. It has been demonstrated that, compared to the CCI, the HRQL-CI possessed greater explanatory power for the HRQL as the outcome variable among general population as well as in a subset of asthma patients [41].

Further investigations are necessary to validate externally this new index's performance in predicting other types of healthcare related outcomes, different data sources, and different disease specific populations, and to determine whether this index does outperform the CCI or its competing indices, such as the EI and CDS [33]. Also, the way to combine two sub-parts of indexes into a set of index is needed to explore, in order to practically being applied in clinical setting in the future.

Medicaid beneficiaries are unique in terms of comorbidity research as the beneficiaries comprise of a vulnerable population usually affected by multiple medical conditions. Medicaid plans cover lower income, more ethnically diverse populations and have higher percentages of participants with chronic illness, multiple chronic conditions, disabilities, severe mental illness, and substance use disorders than commercial plans [42]. All of these factors can influence adherence to quality standards, making it difficult to generalize findings from studies of Medicare and commercial plans to those serving Medicaid populations [43-47]. Co-occurring physical and behavioral disorders, which increase the complexity of treatment and raise the risk of adverse events, represent a particular challenge for providers [47].

The Medicaid program covers a substantial percentage of individuals with diabetes. Medicaid covered about 15% of all individuals with diagnosed diabetes in the U.S. in 2005[48]. The prevalence of diabetes in the Medicaid population was almost twice compared to that in the U.S. population. A recent study indicated Medicaid population where the prevalence of diabetes is 8%, compared to 4% in the general U.S. population. These beneficiaries account for a substantial portion of Medicaid program costs, where much is due to the complications caused by diabetes [49].

In fact, diabetes disease was the seventh leading cause of death on U.S. death certificates in 2006 and placed patients at high risk of heart disease, blindness, kidney failure, extremity amputations, and other medical or comorbid conditions [50, 51]. Most adults with diabetes have at least one comorbid chronic disease [52] and as many as 40% have 3 or more chronic diseases [6, 53]. Comorbidity among this population has contributed to an increased risk of morbidity and mortality,

which places a significant economic burden and an increased demand for medical resource in health care system. Also, managing multiple comorbid conditions is a challenge task for healthcare providers and patients, which in turn can intensify the risk of being poor clinical outcomes and economic burden to healthcare system.

For clinicians, patients having multiple medical conditions could create considerable management complexity, forcing clinicians to consider and prioritize a large array of recommended care, possibly replacing valuable time in the office visit that could be spent addressing issues which have a greater impact on patient health outcomes, therefore, physicians may have a difficulty to adherent to certain disease-specific treatment guidelines, such as diabetes care, when facing patients with multimorbidity.

Also, comorbidity could be an influential factor in patient self-management of disease, such as medication taking behavior [54-58], but the direction of comorbidity impact needs to be examined further due to inconsistent previous findings. Some studies reported that comorbidity places a significant detriment effect in medication taking behavior, in part because as number of medical conditions increased, medication treatment becomes complex or intensive, which could result in difficulties in compliance, or because other medical conditions, such as depression and arthritis, impair patients' functioning and directly pose significant barriers to complete diabetes self-care tasks, such as medication taking [57-59].

However, research has also shown that increasing comorbidity burden can be associated with higher medication adherence [60]. This may be because patients with a higher number of chronic conditions could be better informed about diabetes and its complications and, therefore, would maintain greater rates of adherence despite their greater medication burden and numerous comorbidities. Also, increased perceived susceptibility and severity due to comorbid condition burden may motivate patients to improve their medication taking behavior.

A possible explanation for these conflicting findings is that comorbidity affects healthcare related outcomes differently depending on the target condition and the nature of the comorbid condition(s) [61, 62]. The theory that different types of comorbidities have varying impacts on diabetes disease prognosis has been

previously suggested[61], but few studies have empirically examined the separate roles of different types of comorbidities. Comorbidities could be classified based on their clinical presentation (e.g., symptomatic versus. asymptomatic comorbidities) or the relations with index disease under study (e.g., comorbidities with same pathophysiological risk profile and focus of the same disease management plan with index disease). Although research today has begun to differentiate the impact of different types of comorbidities (e.g., separate them in the analysis, rather than sum them up into a single score), a single summed comorbidity index score based on the comorbidities a patient presents is still a commonly approach to define comorbidity. Therefore, there is a research need to uncover underlying dimensionality of comorbidities and then to give insightful investigations about the distinctive effect of different types of comorbidities on healthcare related outcomes that may have been obscured or confounded in previous studies.

In sum, previous research has provided an understanding about the importance of comorbidity in clinicians' and patients' disease-specific management (i.e., clinicians' treatment selection and adherence to disease-specific treatment guideline, patients' medication adherence), and health related outcomes, including healthcare resource use and costs. Conceptually, co-existing medical conditions could influence physician's and patient's approaches to diabetes specific care, which in turn can influence their health related outcomes (i.e., survival, healthcare utilization and cost). This implies that ignoring concurrent disease management may lead to ineffective control of disease-specific risk factors and miss opportunities to improve patients' functioning, quality of life, and mortality risk. This could in turn reduce economic burden due to caring for these disease populations in the health care system. Clinicians and healthcare policymakers seeking to improve disease-specific management such as diabetes care must address the way in which patients' other concurrent medical problems affect their primary disease that is intended to be treated.

In order to understand and adjust for the impact of comorbidity in health related behaviors and outcomes, an appropriate approach to assess comorbid conditions is essentially required. Because the selection of comorbidity measures in

part depends on a target disease population (seen as an index disease under study) and health outcome of interest, a research is needed to compare predictive performance of alternative comorbidity measures across a spectrum of healthcare related outcomes for a given disease population, to determine an appropriate measure when studying a given health outcome in a particular population. However, we are unaware that predictive performances of existing comorbidity measures have been studied extensively across different healthcare related behaviors and outcomes for a given population.

Moreover, the evidence that comorbidities influence on healthcare related behaviors from health provider's side (e.g., physician's compliance to treatment guideline) and patient's side (e.g., medication adherence) seems to be flimsy due to few research investigations and controversial previous study findings. So, exploring the impact of comorbidities on healthcare related behaviors is an infant area in need of further research. Particularly, given an increasing attention on disease management, understanding and controlling for comorbidity impact on healthcare related behaviors is critical.

Some inconsistent findings regarding comorbidity influence may be in part because of lack of accounting for underlying dimensionality of comorbidities. Differential impacts of different types of comorbidities might be veiled when comorbidity is simply measured as a summed comorbidity index score, which is a common approach to date. Understanding dimensionality of comorbidities is essential knowledge to develop approach to differentiate the impact of different types of comorbidities and further to justify and control for differential influences among them appropriately in the healthcare services research. Therefore, investigating the dimensionality of comorbidities is the next research stage for comorbidity study.

Furthermore, although the importance of weighting scheme in justifying relative influence of comorbidities in a given index has been recognized, approaches in obtaining weighting schemes are unrepresented. The weighting scheme taken directly from original research (usually, weights are each as an integer point value) and weights estimated based on study own population by applying the weighting

estimation procedure in the original research are two common ways to obtain weights. Further research is in need of exploring other potential ways to generate weighting scheme and demonstrating comparative performance of alternative weighting schemes for guiding comorbidity index users further.

1.2 Nature of the Research Project

This dissertation is a theoretically based longitudinal study using patient data from the MarketScan™ Medicaid database from year 2003 to 2007. Type 2 diabetes patients are specifically targeted for this investigation.

Conceptually considering two aspects of dependent variables, which are health related behaviors (i.e., patient medication adherence) and outcomes (i.e., health care utilization), our theoretical model (Figure 1) was built upon the modification of the Health Belief Model by Becker and Maiman [63] and the Aday-Anderson model [64] for health care utilization as proposed by Balkrishnan [65]. The modified Health Belief Model explains social and behavioral determinants of medication use behavior (adherence) with healthcare and medical recommendations [63]. The Aday-Anderson model is used to explain healthcare utilization as a function of three aspects of factors, namely predisposing, enabling and need-related factors [64].

Our theoretical model begins with assuming that patients' willingness to undertake health related behaviors is determined by their health-related perceptions of severity, susceptibility, benefits, and barriers, based on the HBM [65]. Our framework only incorporated the end of product in the HBM- willingness to perform a certain health related behavior. So, we were under the theoretical assumption that one's health-related perceptions of severity, susceptibility, benefits, and barriers have attributed to individual willingness to undertake the behavioral action, and therefore we did not attempt to assess overall HBM model in current study. Also, as proposed by Becker and Maiman [63], one's readiness to undertake health behavior is related to three aspects of factors, including predisposing characteristics (i.e., age and ethnicity), need characteristics (i.e., comorbidity) and

enabling characteristics (i.e., insurance status). Further, these factors can influence health outcomes (i.e., healthcare costs) directly as well as indirectly through health adherent behaviors (i.e., patient's medication adherence and quality of care). This combined conceptual model has been applied in explaining health outcomes in type 2 diabetes patients [63].

In the present study, predisposing factors are age, gender, and ethnicity/ race. Need characteristics are represented by comorbidity measures and diabetes disease severity. Enabling characteristics consist of two aspects, including therapy- and access-related factors. Therapy-related factors are the type of dosing regimen, changes in dosing regimen, treatment/medication naiveness, and the number of medications. Access-related factors include health insurance status, the type of health plan, and the source of care. Medication use behavior is the adherent behavior to chronic medication, which is defined by medication possession ratio using refill patterns of oral anti-diabetic medications. Physician's adherence behaviors are represented by physician's adherence to recommended diabetes quality of care indicators, such as whether or not to routine HbA1c testing was prescribed at last twice per year. Health outcomes have two general types: healthcare resource utilization (e.g., hospitalization and emergency room visits) and healthcare cost (e.g., total costs and diabetes-related costs). These variables are chosen because their predictive ability in medication adherence behavior and healthcare outcomes has been demonstrated in previous research [66]. The following figure 1 captures the theoretical model in this study.

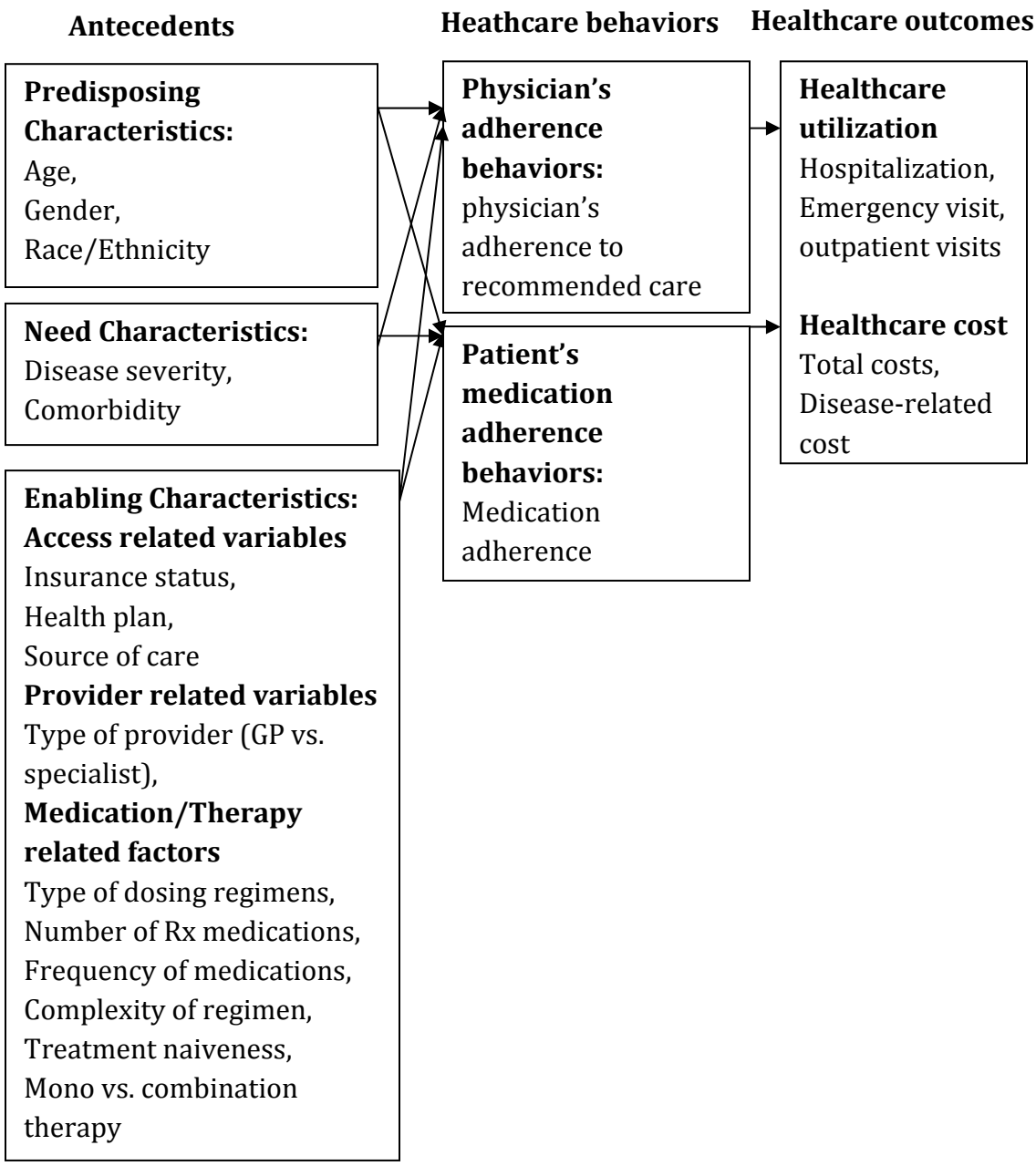


Figure 1 Conceptual Framework

1.3 Study Objectives

This dissertation undertook three objectives. The first one was to assess and compare the performance of Charlson Comorbidity index, Elixhauser index, Chronic Disease Score, and HRQL-comorbidity index in predicting health related behaviors, and healthcare related outcomes in Medicaid receipts with type 2 diabetes. The second was to assess and compare discriminative performance of these comorbidity indexes in healthcare outcomes. We expected to demonstrate relative performances of individual comorbidity index across different healthcare outcomes because previous research suggested that the performance of comorbidity measure varies in the context of healthcare outcome. For a given outcome of interest, we compared these comorbidity indexes' performances to identify most valid comorbidity measure for a given outcome.

Third, we investigated the dimensionality of comorbidity candidates from the HRQL-CI index to identify potential comorbidity structure and then compare our multi-dimensional comorbidity structure with uni-dimensional and two-dimensional comorbidity structure in regard to their model fit and predictive performance in healthcare outcomes. Based on uni-dimensional comorbidity structure in which all comorbidity candidates were presumed to be indicators of a single, unitary propensity to experience comorbidities, one's illness burden was estimated as a single summative comorbidity score. According to the original HRQL-CI index, which consists of physical and mental parts of indexes, two-dimensional comorbidity structure was evaluated in which 15 comorbidities were presumed to reflect physical domain of comorbidities and 10 comorbidities were presumed to reflect mental domain of comorbidities. We hypothesized that our multi-dimensional comorbidity structure, which accounts for differential characteristics of comorbidity candidates, provides better model fit and predictive performance. Also, we expected to demonstrate differential impacts of individual comorbidity dimensions for a given healthcare outcome.

1.4 Significance of the Research Project

Measuring patients' co-existing medical conditions and understanding their role in health related behaviors and outcomes are important from clinical, healthcare policy, and research perspectives. Particularly among type 2 diabetes patients, it has been shown that concurrent diseases can have profound effects on health related behaviors, such as physician treatment selection and patient medication adherence, and subsequently could intensify patients' risk of morbidity, mortality, and higher healthcare resource utilization.

From the clinicians' stand point, comorbidity can serve as a prognostic factor to assess the prognosis of disease conditions and to identify patients at risk of morbidity and mortality. Also, it has been realized that concurrent disease management can lead to effective control of disease-specific risk factors and to improve patients' functioning, quality of life, and mortality risk. However, co-managing multiple medical condition needs can far exceed the time available for patient-provider visits and unfortunately there is few disease-specific care guidelines developed in the context of comorbid conditions to guide healthcare providers managing patients' multiple treatment demands. Therefore, there is a need for a practical tool for assessing comorbid conditions, in terms of being feasibly used to predict patients' clinical outcomes in practice. Such a tool can help physicians to identify patients at risk of poor health outcomes and to prioritize treatment goals and plans given a patient's comorbidities and risk factors, when current guidelines are yet to be developed in the consideration of co-management of patient's multiple medical conditions.

In the health policymakers' point of view, given a fixed healthcare budget, resource allocation needs to take into account patients who are more likely to be at risk of economic burden, such as type 2 diabetes. Understanding the effect of comorbidity on health care outcomes, such as utilization and costs, is essential to gain insight into future health care demands of patients with diabetes.

In order to efficiently allocate medical resource and to minimize potential economic crisis, there is a need to routinely monitor patients with respect to

comorbidities. A comorbidity measure could serve as an essential forecasting tool to identify patients at risk of high health care demands because comorbidity appears to be a strong predictor in estimating future health care demands.

Moreover, with growing demands for quality of care improvement in chronic diseases, healthcare system managers cannot avoid addressing the ways in which patients' other chronic health problems affect their disease-specific care. For example, the current single-disease approach of integrated diabetes care could be extended with additional care modules, both generic and disease –specific, in order to meet the complex health care demands of patients with diabetes. Optimization of disease-specific health outcomes thus, requires a more holistic approach, where comorbid illness must be co-managed. In this regard, a comorbidity measure can serve as a filter to identify patients with comorbid condition burden, therefore, further interventions can be developed specifically tailoring or targeting these patients to improve their quality of care.

From the health outcomes researchers' perspective, since comorbidity can affect the moment of disease detection, prognosis, therapy, and outcome, it has been emphasized that the failure to classify and analyze comorbid diseases could lead to many difficulties in medical statistics [66-69]. More explicitly, there are at least four reasons for researchers to measure or control for one's comorbid conditions. The first reason is to be able to correct for confounding, and thus improve the internal validity of health outcomes research. The second reason is to be able to identify effect modification. The third reason is the desire to use comorbidity as a predictor of study outcome or natural history. Finally, a comprehensive comorbidity measure, including many co-occurring comorbid conditions in one valid variable, is needed for reasons of statistical efficiency.

Therefore, with growing recognition of the importance of comorbidity measurement in health outcomes research, comorbidity measures are required as a risk-adjustment tool for statistical efficiency in the analysis and a predictive indicator of patient health outcomes. However, because no gold standard approach of assessing comorbid conditions exists, various comorbidity indices appear in the literature today, which vary in disease specific population and health outcomes of

study interest. To further guide health outcomes researchers in assessing and controlling comorbid conditions, for a given disease population, there is a research need to extensively examine relative performances of alternative comorbidity measures in predicting a variety of health outcomes and to conceptually assess the impact of comorbid conditions on health related behaviors, such as physician's adherence to treatment guidelines and patient's adherence to treatments, and in turn on health related outcomes.

Chapter
2. Literature Review
2.1 Comorbidity
2.1.1 Prevalence of Comorbidities

The aging of population is a worldwide phenomenon. In 1990 the proportion of those 65 years or over ranged from 11% to 18% in Japan, Western Europe, North America, and Australia, which is expected to increase to approximately 19-26% in 2025 [70]. Because many health problems are known to increase with age, this demographic trend may lead to an increase in the absolute number of chronic conditions in the population. There is a growing body of evidence that older people are at risk for multiple, comorbid conditions, so the prevalence of comorbidity in the general population, as well as among those seeking health care, will probably also increase and becomes a common phenomenon. It has been shown that 57 million Americans had multiple chronic conditions in 2000 and that this number will rise to 81 million by 2020 [1], with a consistent trend worldwide [2-6]. As estimated, patients aged 65 years and older present with 2.34 chronic medical conditions [5]. In fact, 50% of patients with a chronic disease have more than one medical condition [71].

In response to this phenomenon, health care increasingly needs to address the management of individuals with multiple coexisting diseases, who are the norm rather the exception [72]. In the United States, about of 80% of health care spending is devoted to patients with 4 or more chronic conditions, with costs increasing exponentially as the number of chronic conditions increases [6].

2.1.2 Definition of Comorbidity

2.1.2.1 Nature of the Health Condition

To define and conceptualize patient's co-existing medical conditions, it is essential to understand the nature of the health condition. The nature of the conditions that co-occur have variously included diseases [2, 7], disorders [73], conditions [2, 7, 74, 75], illnesses [76], or health problems [77]. Some of these terms and concepts can be linked to classification systems, such as the International Classification of Disease (ICD), the Diagnostic and Statistical Manual of Mental Disorders (DSM), or the International Classification of Primary Care (ICPC), but the same is not possible for other terms and concepts, making it difficult to use them in a reproducible manner.

Distinguishing the nature of the health conditions is critical because simultaneous occurrence of loosely defined entities may signal a problem with the classification system itself [78, 79]. For instance, one may view that depression and anxiety are not different entities but part of a spectrum, and, if so, patients with both conditions should not be classified as having comorbidity.

2.1.2.2 Definition, Chronology and Typologies of Comorbidity

Comorbidity is most often defined in relation to a specific index or primary condition [4], as in the seminal definition by Feinstien (1970): "Any distinct additional entity that has existed or may occur during the clinical course of a patient who has the index disease under study."[7] Which condition should be designated the index and which the comorbid condition is not self-evident and may vary in relation to the research question, the disease that prompted a particular episode of care, or of the specialty of the attending physician. A related notion is that of complication, a condition that coexists or ensues, as defined in the Medical Subject headings (MeSH)-controlled vocabulary maintained by the National Library of Medicine (NLM).

Beyond this essential definition of comorbidity, research today has explored the characteristics of comorbidities more detail regarding the time frame used to define comorbidities [80] and general typologies of comorbidities [61], in order to better measure them and assess their impact on healthcare management. Specifically, the presentation of comorbidities can vary in the time frame over which they are defined and in the characteristic dimensions.

First, regarding the chronology of comorbidities, time span and sequence are the relevant considerations. The first refers to the span of time across which the co-occurrence of 2 or more conditions is assessed. This concept may either be implicit or explicit in requiring that the various clinical problems co-occur at the same point in time. Synchronous occurrence has not always been the focus in the study of co-occurring mental health conditions, however, where there has been a considerable interest in disorders co-occurring across a period of time but not necessarily at the same time (Figure 2(a))[80].

A distinct but related issue is the sequence in which comorbidities appear, which may have important implications for genesis, prognosis, and treatment. Patients with established diabetes who receive a new diagnosis of major depression may be very different from patients with major depression who are latter have diabetes diagnosed, although from a cross-sectional perspective, both may be viewed as patients with diabetes and depression (Figure 2 (b))[80].

Second, research has identified three general typologies of comorbidities, including *clinically domain conditions*, *concordant versus discordant chronic conditions*, and *symptomatic versus asymptomatic chronic conditions* [61].

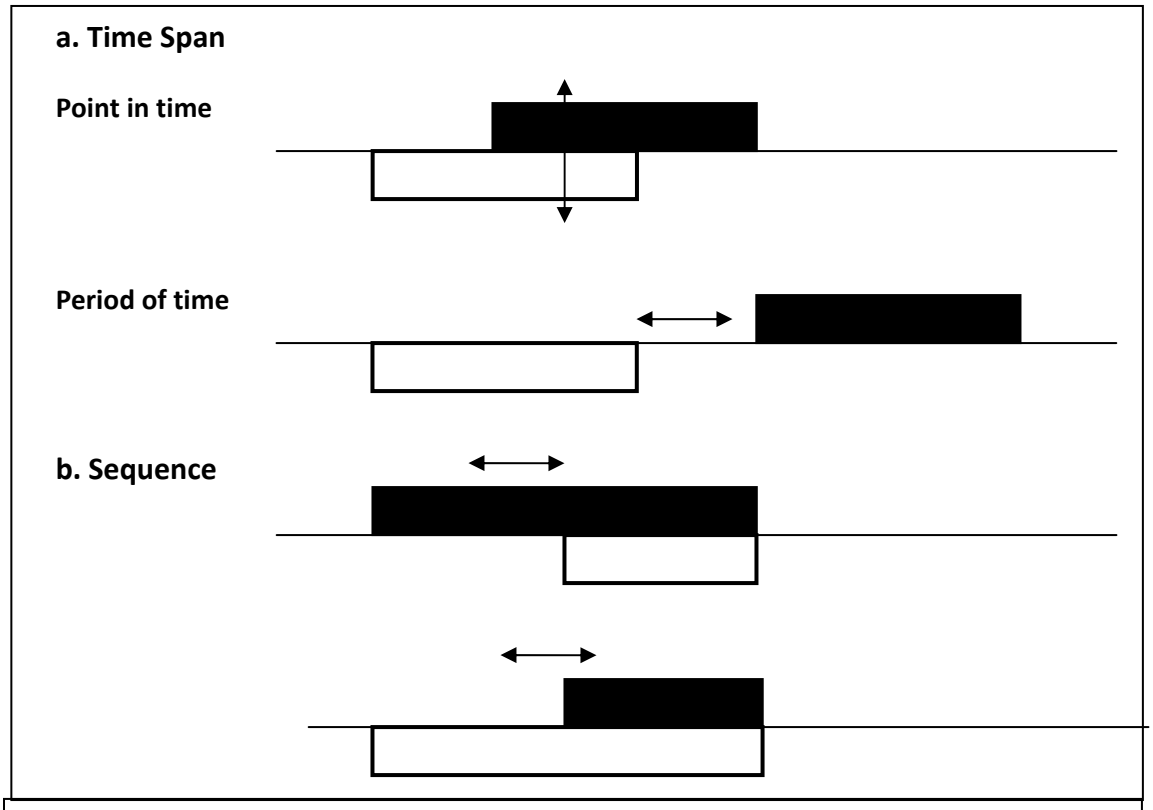
Clinically domain conditions refer to the comorbidities that are so complex or serious that they eclipse the management of other health problems, including end-stage disease (i.e., metastatic renal cell carcinoma), severely symptomatic disease (i.e., class IV chronic heart failure), and recently diagnosed disease (i.e., breast cancer) [61].

Concordant conditions represent parts of the same overall pathophysiological risk profile and are more likely to be focus of the same disease and self-management plan. *Discordant conditions* are not directly related in either their pathogenesis or

management [81]. An example of diabetes as the index disease, *concordant conditions* are like hypertension, coronary artery disease, peripheral vascular disease, while *discordant conditions* with diabetes are like chronic low back pain, prostate cancer, and asthma.

Symptomatic condition refers to showing signs or symptoms of a disease or condition, whereas it is considered *asymptomatic* when a person has an illness and is not showing symptoms. *Symptomatic conditions* are like depression, rheumatoid arthritis, gastroesophageal reflux disease, angina, while *asymptomatic conditions* are like hypertension, hyperlipidemia, and moderately poor glycemic control. Treatment for *symptomatic conditions* is more likely to focus on improving patients' symptom profile, functioning and quality of life, and may also delay or prevent poor long term outcomes, while treatment for *asymptomatic chronic conditions* tends to focus almost exclusively on preventing downstream adverse events and early mortality [61].

Considering these chronologies and typologies of comorbidities is important for comorbidity research because the presentation of comorbidities being studied may vary in time frame over which to assess them and their time sequential relationship with an index disease, and, therefore, have differential impact on health related outcomes. Also, comorbidities with distinct characteristics may differentially influence how health care systems, clinicians, and patients approach their management specific to the index disease. Clearly, understanding and defining these characteristics of comorbidities is an essential step of measuring comorbidities and studying their impact on health outcomes.



Each block represents the duration of a different comorbid disease. Two comorbid diseases can either be present at the same point in time (vertical arrow), or occur within a given time period without being simultaneously present at any given point in that period (horizontal arrow) (a). Irrespective of the selected time span, the sequence in which the disease appear is of particular interest in the study of etiological association (b)

Figure 2 Chronologic Aspects of Comorbidity

Source: [80]

2.1.2.3 Terminologies related to Comorbidity

One problem in comorbidity research is that several terminologies related to comorbidities appear to be used interchangeably with comorbidity, and, however, most of them are conceptually different, resulting in some confusion in comorbidity research [82]. These relevant terms include multimorbidity, morbidity burden, and patient complexity.

First, multimorbidity has been increasingly used to represent "co-occurrence of multiple chronic or acute diseases and medical conditions within one person" without any reference to an index condition [83]. Dual diagnosis in psychiatry would be a particular example of multimorbidity, where two distinct disorders co-exist without any implicit ordering, e.g., severe mental illness and substance abuse [2](Figure 3).

To date, the terms of comorbidity and multimorbidity often seem to be used interchangeably. However, it must be clear that, by definition, the simultaneous presence of multiple health conditions is known as *comorbidity* when there is an index condition and other related or unrelated conditions (concurrent or disconcurrent conditions) [7], and as *multimorbidity* when no one condition is identified as an index condition [2]. Proponents of the concept of multimorbidity tend to focus on primary care, a setting where the identification of an index disease is often neither obvious nor useful [2]. For the purpose of this dissertation, the term "comorbidity" will primary be focused and defined according to Feinstein's definition, which refer to "any distinct additional entity that has existed or may occur during the clinical course of a patient who has the index disease under study."[7]

Another more broad relevant term is that of morbidity burden, which is determined by the presence of the different diseases, their relative severity, and any health related attributes from that individual patient, such as age and gender. Finally, a newly emerging construct is that of patient's complexity. This acknowledges that morbidity burden is influenced not only by health-related characteristics from the person himself, but also by non-health related attributes

from outside of that person, such as socioeconomic, cultural, environmental and patient behavior characteristics [84, 85]. From a clinical perspective, it will be obvious that disease factors interact with social and economic factors to make clinical management more or less challenging, time-consuming, and resource intensive. Capturing and measuring this complexity overall, however, remains a challenge.

To integrate these conceptually different, but relevant terminologies, one illustrative example is given that of a 60-year-old woman with diabetes mellitus, hypertension, and depression, who is from an ethnic minority, has a low literacy in English, and who cares for her stroke-limited husband. Her rheumatology health professional, focusing the diabetes mellitus as a primary or index disease, would consider her hypertension and depression as comorbidities. Her primary care physician might describe her as having multimorbidity, giving equal attention to her diabetes mellitus, hypertension, and depression. Her morbidity burden would be determined by the presence of the different diseases, their relative severity, sex, and age. The terms of comorbidity, multimorbidity, and morbidity burden, all are conceptual attributes of patient complexity but they are distinct regarding representation of patient health conditions. These terminologies need to clearly be disentangled and defined from patient complicated medical conditions so the impact of comorbid conditions in health related outcomes can accurately be assessed.

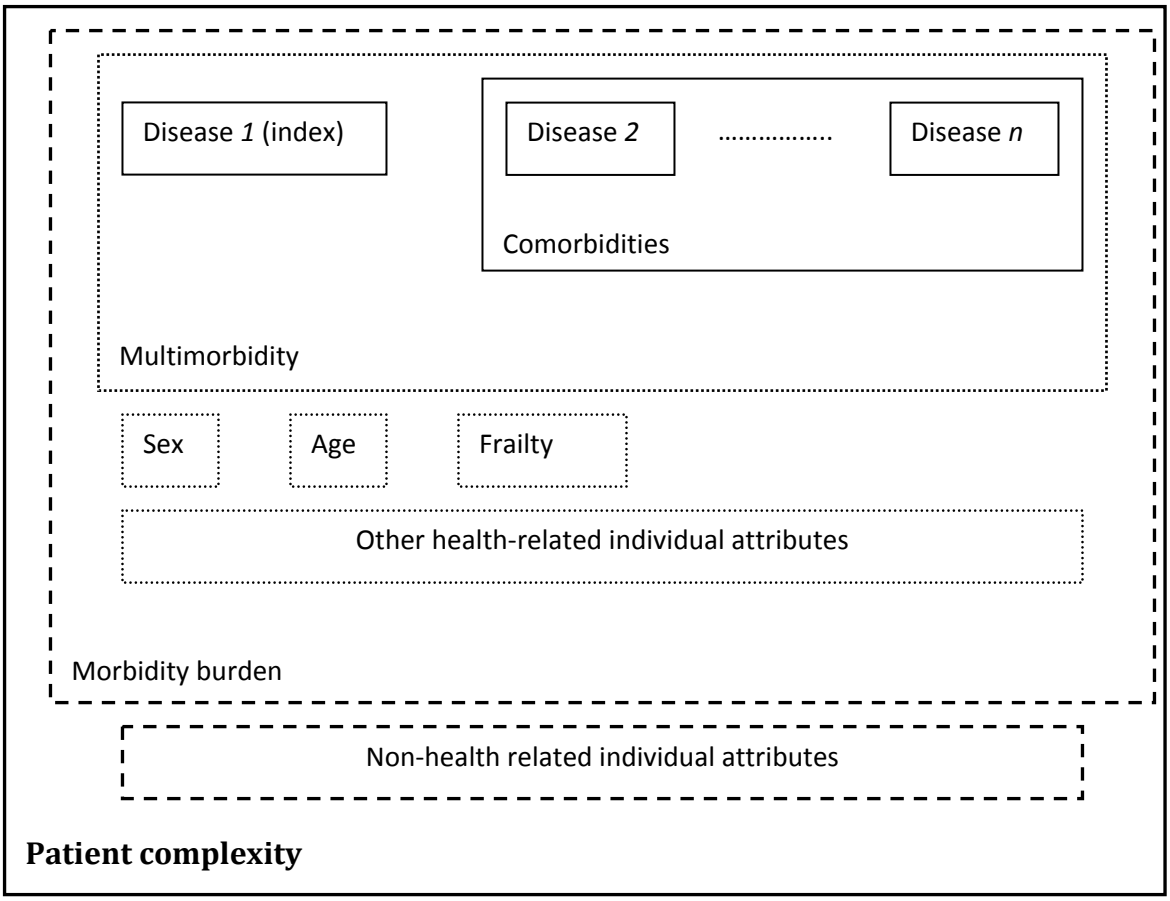


Figure 3 Constructs of Patient Complexity

2.1.3 Etiology of Comorbidities

Due to considerable prevalence of comorbid conditions in the aging population and their profound impact on disease management, underlying phenomenon of comorbidities has been called for analysis, in order to given more specific recommendations for further research, public health and health care practice. Particularly, the coexistence of two or more diseases in the same individual raises two clinical questions: whether there is an underlying common etiological pathway, and/ or what is their impact on clinical care. The review in the following describes potential underlying etiology of comorbidities, in terms of their causes, associations between them, and their consequences.

2.1.3.1 Potential Causes of Comorbidities and Their Pathways to Comorbidities

Gijsen et al's study (2001) was conducted to accumulate and summarize the available research evidence on the causes and consequences of comorbidity of a wide range of chronic somatic diseases [8]. Based on their search strategies[1], eighty two studies of comorbidity were included, where patients with cardiovascular diseases were most frequently studied as an index-disease (48%), followed by cancer (23%), musculoskeletal diseases (13%) and diabetes mellitus (11%). Along with Figure 4, potential causes identified were intra-personal factors, such as demographics, genetics, biological risk factors, and inter-personal factors, such as physical and social environments and health care system.

How these potential factors influence comorbid conditions can be explained by four etiological models, including *direct causation, associated risk factors, heterogeneity,* and *independence*, for a given simple illustrative situation in which

[1] A search was performed of the Medline databases from January 1993 through December 1997. The keyword 'comorbidity' or a related term (such as comorbidity, multiple pathology, disease clustering, multimorbidity) was included as search criterion. Final articles were included if one of the selected disease groups was an index-disease and study outcome included mortality, functional status, quality of life, or health care.

there are only 2 conditions. (Figure 5) In fact, these four models are not necessarily mutually exclusive and have yet to be applied extensively to the study of comorbidity. All models have, however, been successfully tested by means of simulation and proved empirically valid in the assessment of selected comorbidities [86].

First, in the *direct causation model*, the presence of 1 disease is directly responsible for another. From a clinical perspective, this model would also include the situation in which treatment for 1 disease caused another condition (e.g., an anticoagulant given for atrial fibrillation causing a gastrointestinal hemorrhage)

In the *associated risk factors model*, the risk factors for 1 disease are correlated with the risk factor for another disease, making the simultaneous occurrence of the diseases more likely. For example, smoking and alcohol consumption are correlated; the former is a risk factor for chronic obstructive pulmonary disease and the later a risk factor for liver disease, making it more likely the 2 diseases will occur together.

By contrast, in the *heterogeneity model*, disease risk factors are not correlated, but each is capable of causing diseases associated with the other risk factor (e.g., tobacco and age are independent risk factors for a number of malignancies and cardiovascular diseases).

In the *independence* (distinct disease) model, the simultaneous presence of the diagnostic features of the co-occurring diseases actually corresponds to a third distinct disease. For example, the co-occurrence of hypertension and chronic tension headache might both be due to pheochromocytoma.

Understanding the factors, which can attribute comorbid conditions, and how they impact on comorbid condition is essential, in order to prevent risk of being comorbidity burden and consequently to better manage their impact on health related outcomes.

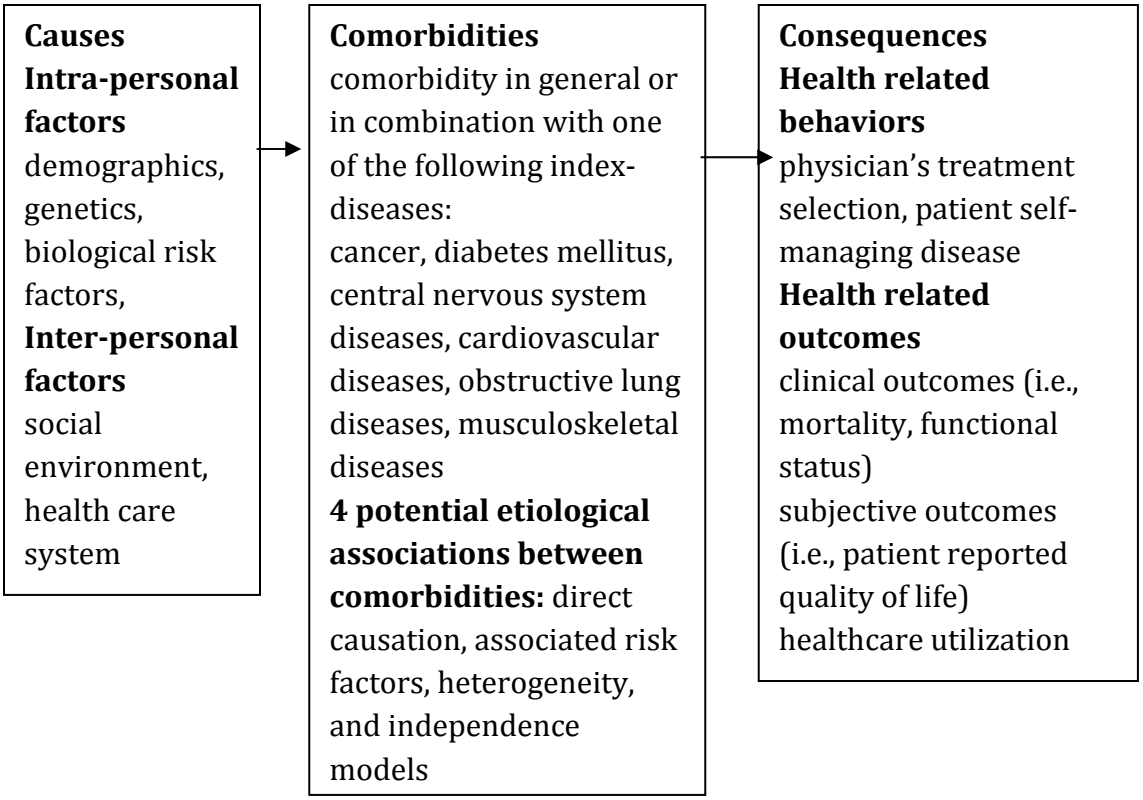
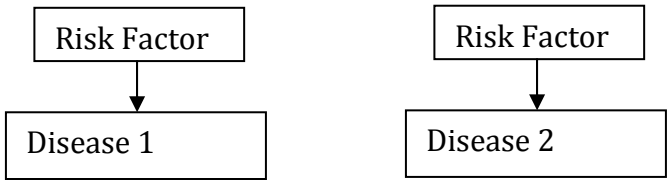
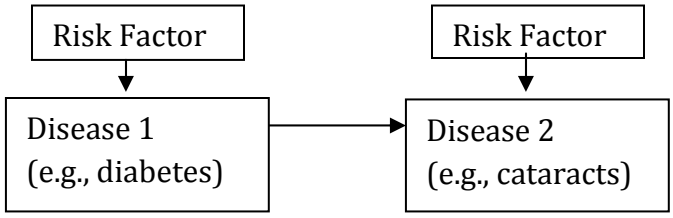


Figure 4 Conceptual Model Describing Comorbidity, Its Causes and Consequences

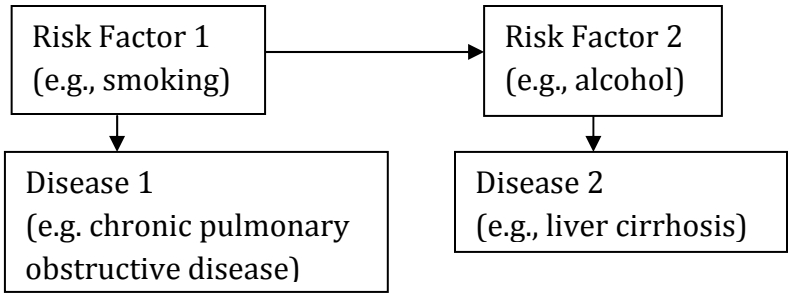
No etiological association: there is no etiological association between the diseases



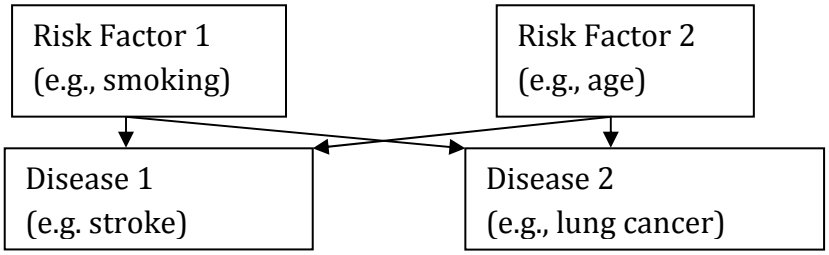
Direct causation: one of the diseases may cause the other



Associated risk factors: the risk factors for each disease are correlated



Heterogeneity: the risk factors for each disease are not correlated,
but each one of them can cause either disease



Independence: the presence of the diagnostic features of each disease is actually due to a third distinct disease

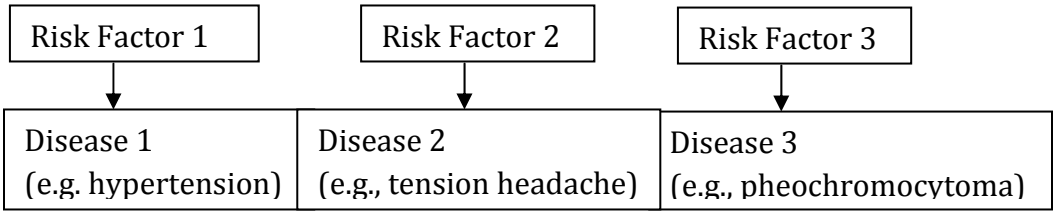


Figure 5 Etiologic Models of Comorbidities

2.1.3.2 Consequences of Comorbidities

Also, based on Gijsen et al's study (2001) [8], potential outcomes, which can be affected by comorbidity, are health related behaviors, such as physician's treatment strategies [87-95] and complications of treatment [23-25, 88, 96-114], health related outcomes, such as mortality [87, 88, 101-105, 115-117], functional status or quality of life [118-141], health care utilization (i.e., the length of stay, discharge dispositions or admissions) and costs [129, 137, 142-146], frequently after adjustment for a large variety of covariates, including clinical variables [8] (Figure 4).

Gijsen et al (2001) [8] concluded that, in different settings, with different study designs and outcome measures, and even after adjustment for different confounders, comorbidity in general does affect health outcomes. Particularly, their study found that there are some consistent results across comorbidity research. First, diseases that affect systems that are essential for maintaining physiological homeostasis (cardiopulmonary and renal system) were significantly related to mortality. Second, comorbid mental disorders were significantly associated with functional status or quality of life. Third, comorbidity was consistently related to health care utilization (costs, length of hospital stage, and number of physician visits). Differences in effect observed between some studies can be explained by the number of patients in the study, the confounders taken into account (such as stage of disease), and other characteristics of the study design (retrospective, prospective or cross-sectional) [8].

2.1.3 Comorbidity Measures

Because studies of comorbidity or multimorbidity reveal that there is no consensus about how the co-occurrence of diseases should be measured [147], various approaches have been taken to characterize the combined burden of pre-specified diseases or conditions as a single measure on a scale. These approaches vary in the analytic strategy for measuring comorbid conditions and the type of data

sources available to construct comorbidity index. In general, three different strategies and four data sources regarding the construction of comorbidity index appear in comorbidity research today. The review below describes advantages and disadvantages of each of these strategies and data sources and gives an example of relevant comorbidity measure. (Table 1)

The simplest comorbidity measures provide an ordinal comorbidity score by a sum of the number of diagnoses from among a list of candidate diagnoses [147-150]. This method has the advantage of conceptual simplicity and ease of data ascertainment. Some authors used ICD-9 codes to count the total number of comorbid conditions to examine the prevalence of comorbidity [147-149, 151], whereas others made up a list of carefully selected comorbid conditions and counted the number of these conditions present, by using medical records or ICD-9-CM codes, for the purpose of studying relationships between comorbidity and health related outcomes [33, 152, 153]. An example of such measures is the Functional Comorbidity index, a self-administered index recently developed by Groll et al (2005) using a North American population affected mostly by orthopedic problems and specifically for applying in the general population with physical function. This index is an 18-item list of diagnoses, each of which is given 1 point if present, and the final score is simply a sum of the diagnosis present. It is aimed to predict health related outcomes specific to physical aspect of health-related quality of life [150].

However, because all diagnoses are scored equivalently, implicit in this strategy is the assumption that all comorbid conditions have a similar effect, and that their overall impact on patients' lives is driven primarily by the number of conditions being managed. Such measures may capture the overall burden of illness, but they cannot identify the characteristics of comorbid conditions that influence how patients and clinicians make decisions about the index disease treatments. This strategy ignores the fact that different diseases and their severity may affect the outcomes of interest differently. The second analytic strategy, which is to obtain a summative weighted score of comorbidities, has been developed to address this problem.

Comorbidity indices first identify the present comorbid conditions and subsequently apply weights or pathophysiological severity ratings for these diseases. The comorbidity measure then weights the contributions of different diseases, depending on their role in the analytic relationship with an index disease. An example of such measures has been developed by Charlson (1987) [20]. The so-called Charlson Comorbidity Index (CCI) (Table 2) is a weighted index of comorbidity in which the weights are based on the observed association with 1-year mortality risk in a cohort of hospitalized patients. The index assigns a weight of 1 to 6, according to the risk of mortality, to each of the 19 defined comorbid conditions. The CCI is the sum of the weights for each comorbid condition. It is mainly useful in studies with mortality as outcome variable and in which the occurrence of diseases is assessed by interview, anamnesis, medical examination or screening of the medical charts. Studies have found that the CCI was significantly associated with various health outcomes, including in-hospital mortality [154, 155], post-discharge all-cause mortality [20, 156], and healthcare expenditures [157].

However, such a weighting scheme has three disadvantages. First, there is an issue regarding the specification of the weighting scheme. The weighting scheme can be taken directly from original index or driven specifically from study population by applying the same procedures for developing original weighting scheme into study population to get study specific weight estimates, which is commonly called study specific weights. Previous research has shown that the predictive performance of comorbidity index was enhanced if investigators used study specific weights, instead of the original weighting scheme, raising questions as to what weighting scheme to use [26, 40]. However, such study specific weighting scheme may overly be customized to specific disease population and to a given health outcome of interest, and, therefore, such a study weight based index will be less useful when applied into other settings (i.e., other index diseases and health related outcomes).

The second disadvantage of a summed measure, regardless of whether they are based on simple counts or a sum of individually weighted conditions, is that it ignores potentially important relationships between diseases that might differ from

their simple sum. For example, the interaction between chronic obstructive pulmonary disease and congestive heart failure might exceed the simple sum, whereas cardiovascular disease related to diabetes might be overweighed in an index that counts both independently. In the other words, these summative measures only assume an additive relationship for the included diseases, and, therefore, less address underlying etiologic associations between comorbidities.

Lastly, these summed measures often force a linear relationship with the ordinal scale across its entire range. A patient moving from zero to one comorbid disease could realize the majority of the comorbidity effect, with additional unit increases having a diminishing impact. The third strategy, which is categorizing summed scores, rather than treating the index as an ordinal variable, can address this disadvantage.

Categorizing summed measures focus on the stratification or classification of patients into groups according to disease and conditions, age, and sex, rather than only rely on present specific diseases. This strategy acknowledges that individual diseases counted separately in an index might arise from a common cause, whether that cause is exogenous (e.g., tobacco smoke) or endogenous (e.g., inflammatory response). Examples included the Adjusted Clinical Groups (ACGs)[158], Diagnosis-Related Groups (DRG)[159], Healthcare Resource Groups (HRGs) [160], and Aggregated Diagnosis Groups (ADGs)[2][161].

However, these classification measures are relatively new and have only recently started to be used to adjusted capitation payments in the US [162-164]. Hence, we have limited knowledge about the extent to which they predict other

[2] Each ICD-9 diagnosis code for each patient is mapped to one of 32 diagnosis groups known as ADGs. Diagnoses within the same ADG are of similar severity and expected need for health care resources over time. These diagnosis groups are clustered according to the following clinical characteristics: (i) duration of the condition (acute, recurrent or chronic); (ii) severity of the condition (e.g. minor and stable versus major and unstable); (iii) diagnostic certainty (symptoms versus documented disease); (iv) a etiology of the condition (infectious, injury or other); and (v) likelihood of specialty care involvement (medical, surgical, obstetric, haematology, etc.).
Patients are assigned to an ADG if they have one or more of the ADGs constituent diagnoses and, hence, each patient may have between zero and 32 ADGs. Each individual can also be assigned a single mutually exclusive ACG, which is derived from a combination of age, sex, presence of specific ADGs, number of major ADGs and total number of ADGs. The ACG groupings contain individuals with similar needs for health care resources based on overall expenditures. Patients with similar predicted (or expected) overall utilization may be assigned different ACGs if they have different epidemiologic patterns of morbidity.

types of health outcomes and whether these tools improves the equity of resource allocation or the efficiency of health services. In addition, these tools often are based on data derived from computerized patient records or from the billing records of insurance companies. They therefore suffer from problems such as incomplete or inaccurate coding of diagnostic data.

Another way to classify existing comorbidity measures is based on data sources which are available to construct comorbidity index. Four types of data sources commonly used by comorbidity research are medical records, patient self-reports, clinical judgments, administrative dataset. Each type of dataset may bring several advantages and disadvantages to comorbidity research.

First, many comorbidity indices rely on medical records. In general, comorbidity indices, which are commonly constructed based on medical records, could be classified into two types: one based on a list of selected disease diagnose, such as the CCI [20]; another one based on specific bodily organ systems, such as the Cumulative Illness Rating Scale (CIRS) [9], the Index of Co-existent Disease (ICED) [165], and Kaplan Index [11]. An example of body system based indices is the CIRS, which consists of 13 body systems and each is weighted by the severity of impairment affected by comorbid conditions, ranging from 0 (no impairment) to 4 life-threatening impairment. The final comorbidity score based on the CIRS is the sum of weighted impairments of body systems [9].

One advantage of medical records is the good correspondence between diagnosed conditions and the disease entities ordinarily included in comorbidity indices, which assures that the index reflects the target concept. Also, medical records are more likely to reflect the information available to clinicians treating the patients/study participants.

However, reviews of medical records can be a resource-intensive method of data collection. Also, medical record review requires patient consent and consent of the health care provider and/ or the health care organization. Moreover, validation substudies to assure sufficient intra-rater and inter-rater reliability is usually required. Furthermore, medical records must be available over a sufficient period of time to assure that the comorbidity index can be accurately constructed. Lastly,

the quality of the medical record data may be different across different types of clinical settings (e.g., inpatient versus outpatient).

Second, some comorbidity measures have been developed to collect information directly from patients, such as the Comorbidity Symptom Scale [18], Geriatric Index of Comorbidity[166], Total Illness Burden Index [167], and the HRQL index. Other comorbidity indices originally intended to use medical records as the data source have been adapted for patient self-report, such as Katz adaptation of the CCI to patient review[15]. Research has shown that self-report correlates well with data collected medical record review.[168] There are two advantages of patient self-reports compared to medical record reviews. Compared to medical record data collection, self-report information is required less resource for data collection because of patient self-administration of self-report questionnaire of comorbidity measure. Also, self-report information are potential for being more complete because patients can be asked to recall their entire medical history, to gather insights in one's perceptions on the severity of each comorbid condition and their perception of its impact on their function, whereas medical records may be limited to a time period that does not include all relevant history. On the other hand, self-report data can suffer from subjects recall bias.

The HRQL comorbidity index is most recently developed by Mukherjee et al (2009) [41], based on the Medical Expenditure Panel Survey, a nationally-representative public domain dataset. Two lists of 20 and 15 clinical conditions are for physical and mental aspects of health-related outcomes, respectively. The weights were derived from the standardized beta coefficients in the regression analyses where the HRQOL, measured by the Short Form 12 (SF-12), was main outcome of interest. Compared to the CCI, this index has demonstrated greater explanatory power for the HRQOL as the outcome variable in the general population as well as a subset of asthma patients [41].

However, the HRQL comorbidity index needs to further be validated in other types of data sources (e.g.., medical records) and disease specific populations, health care related behaviors and outcomes, and compared to other comorbidity measures. Because the HRQL comorbidity index has been shown as an important predictor of

the HRQOL [41] and the relationships between the HRQOL and healthcare related behaviors (e.g., physician's treatment compliance with diabetes care [169] and patient's anti-diabetic medication adherences [170]) and outcomes (e.g., economic costs [171]) have been demonstrated, one could assume that the comorbidities as measured by the HRQL comorbidity index are important factor in healthcare related behaviors and outcomes. This assumption is worthy further investigated.

For given studies with large populations, or when patients are in hospitals or nursing homes, the cost of patient's interviewing may be prohibitive. Also, cognitive impairment can adversely affect recall accuracy of the data. Moreover, self-report data may suffer from recall bias and other self-report bias, such as social desirability, particularly when included diseases in the index are sensitive to be measured (i.e., HIV disease). These disadvantages could attribute to measurement errors. The greatest concern is that errors in recall or reporting of other study will correlate with errors in recall or reporting of other study variables. These dependent errors can substantially bias estimates of effects.

Third, another comprehensive way to collect comorbidity information is to collect an overall rating of patient's health status from their physicians, such as the American Society of Anesthesiologist Index [172]. The potential advantages of these ratings are: (1) simplicity, which translates to low resource requirements, (2) independence, which precludes dependent errors associated with errors in interview data, and (3) good correspondence with physician impressions that affect medical decision making.

However, such ratings have some potential limitations. The first disadvantage is that their simplicity may mask the true complexity of comorbidity. Second, patient consent will be required to obtain the rating from the physician or to review medical records. If the rating is the only information obtained from physicians directly or from medical record review, then the efficiency of data collection could be poor.

Administrative databases, such as claims datasets and pharmacy databases have been used to construct comorbidity indices. These indices translate information gathered for an unrelated primary purpose to a secondary purpose of

scaling comorbidity. Such translation may not be inevitably imperfect. For example, claims databases may subject to its main purpose of data collection, such as reimbursement, so the information may inflate the burden of comorbid diseases. The quality of the claims data may also be better for inpatient services than for outpatient services. Use of pharmacy databases requires that all participants have uniform access to reimbursement for relevant pharmaceuticals and that all participants used only the pharmacy housing the databases to obtain prescriptions. Specialized expertise is recommended to obtain administrative data and to manipulate them.

The advantages of using administrative data are: (1) fewer resources required collecting comorbidity data than medical record review and patient interview, particularly given very large study populations, and (2) independence of errors in measurement of comorbidity from errors in measurement of other study variables collected by other methods. There are three administrative claims-based comorbidity scores: the ICD-9-CM-based Charlson (or called Deyo adaptation of the CCI [17]) and Elixhauser indexes [33] and the pharmacy claims-based RxRisk score[173] (formerly the Chronic Disease Score [35]).

Like the Deyo-CCI, the EI[33] is an ICD-9-CM coding algorithm to defining comorbid illness. However, compared to the Deyo-CCI[17], where only 17 conditions are included, the EI measures the effect of 30 different comorbidities conditions[33]. The EI distinguishes comorbidities from complications by considering only secondary diagnoses unrelated to the principal diagnosis (index disease) through the use of diagnosis related groups (DRGs). For example, a patient with a claim for congestive heart failure would have this condition coded as comorbidity only if the medical record did not contain a DRG for cardiac disease. The final EI score is calculated as the sum of comorbid conditions present, without applying any weighting scheme like the CCI.[33] In direct comparisons between the CCI and EI, studies showed the EI to be statistically slightly superior to the CCI at adjusting for comorbidity.[37, 38, 174]

However, one disadvantage of the EI is no weighting scheme applied, so the relative importance of each of the 30 comorbidities in the EI cannot be gauged.

Some EI comorbidities may not be importantly associated with some outcomes and may therefore be unnecessary in regression model. In this regard, Walraven et al (2009) constructed a weighting scheme for the EI by using multivariate logistic regression to determine the independent association of each comorbidity with death in hospital [175]. Regression coefficients were modified into a scoring system that reflected the strength of each comorbidity's independent association with hospital death. The study also demonstrated that the weighting based EI score was significantly associated with in-hospital mortality and health services measures associated with burden of illness. In addition, the weighting based EI score was significantly better discrimination for hospital death than the Deyo-CCI score [175].

Pharmacy data represents another source of administrative information from which an assessment of comorbidity can be made. Among pharmacy-based case-mix instruments, the Chronic Disease Score (CDS) has been the most extensively described [35, 173, 176, 177]. The CDS was initially developed by Michael Von Korff and colleagues at the Group Health Cooperative (GHC) with the goal that the score should reflect the number of chronic diseases under treatment, the complexity of the treatment regimen, and the likelihood of disease-related morbidity or mortality [35]. The CDS is a risk-adjusted metric based on age, sex, and history of dispensed drugs, instead of ICD-9-CM codes to classify comorbid conditions. The scoring rules are based on the occurrence of any use of a medication, not the number of times a prescription that was filled, so that persons who adhered to use of the medication regimen or who were given prescriptions that needed to be filled at shorted intervals would not receive a higher score that persons receiving the same prescription who did not adhere to the medication regimen. The original weighting scheme of the CDS was derived through clinical judgments on the impact of each class drug on chronic disease severity [35], while revised CDS weights were the parameter estimates (regression coefficients) for sex, age group, and each of the variables indicating drug use [177] The final CDS score is the sum of weights assigned to present conditions, which are indicated by the occurrence of any one of corresponding medications. The revised weighting CDS score driven by empirical estimation approach has shown improved estimation and

prediction over the original weighting CDS score assigned by clinical judgments [177].

The most recent modifications to the CDS are the RxRisk score for use among general populations [176] and the RxRisk-V score for use among Veterans Affairs populations [173]. There are two weaknesses in the CDS that motivated development of the RxRisk. First, the CDS was developed using the GHC formulary as a basis for drug classification. Researchers and health plan decision makers had applied the model to other data sets but this required developing individual crosswalk. The CDS had not been intended as a capitated payment adjuster and included several categories that are inappropriate in a model used for finance purposes.[3] Second, the CDS was developed and estimated exclusively within the GHC staff model delivery system so risk weights may reflect practice pattern and drug use bias present in GHC, limiting the applicability of the model in a wider setting. The RxRisk system has been demonstrated to predict hospitalizations, mortality and health care costs [35, 176, 177]. Recent comparison study showed that the predictive performances of the CCI and EI in healthcare expenditures were similar, while the RxRisk outperformed both [157].

	Advantages	**Disadvantages**	**Example of Comorbidity measure**
Analytic strategy			
Ordinal scale	• Conceptual simplicity • Ease of data ascertainment	• Assume the impact of each selected diagnosis on health outcomes equivalency • Only assumes an additive relations among comorbidities;	Functional Comorbidity index [150]

[3] Specifically, the "pain" and "pain and inflammation" categories among adults included drugs that are prescribed less systematically than is appropriate for a finance model.

		ignore other potential mechanisms between comorbidities (i.e., interactions) • Forces a linear relationship with the ordinal scale across its entire range	
Weighting	• Addresses nonequivalence and severity of diseases	• Only assumes additive relations among comorbidities • Forces a linear relationship with the ordinal scale across its entire range • Study specific weights may be overcustomizing, which decreases applicability	Charlson Comorbidity Index [20]
Categorization	• Addresses nonlinear relationship	• Often applied in the prediction of healthcare costs and resource use; uncertainty in the prediction of other health related outcomes • Index construction mainly based on administrative data (i.e., claims), so the validity of the measure in part depending on the quality of data	Adjusted Clinical Groups [158], Diagnosis-Related Groups [159]
Data Sources			
Medical record	• Good correspondence	• Resource-intensive for	Cumulative Illness Rating

	between diagnosed conditions and the disease entities ordinarily included in comorbidity • Reflects clinical information	collecting medical record data • Requires various stakeholders' consents (i.e., patients, healthcare providers, organization) • Requires to assure sufficient intra-rater and inter-rater reliability • Requires a sufficient time period over which the comorbidity index can be accurately constructed • Differential quality of medical records by the type of clinical settings (i.e., inpatient vs. outpatient)	Scale [9]
Self-report	• Efficiency of data collection, in terms of more comprehensive information and less resource for data collection	• Recall bias • Social desirability	Comorbidity Symptom Scale [18], HRQOL comorbidity index [41]

Clinical judgment	• Simplicity, which translates to low resource requirements • Independence, which precludes dependent errors associated with errors in interview data • Good correspondence with physician impressions that affect medical decision making	• Patient consent is required to obtain the rating from the physician or to review medical records • The efficiency of data collection will be poor if the comorbidity information only obtained from physicians directly or from medical record review	American Society of Anesthesiologist Index[172]
Claims data	• Fewer resources required to collect comorbidity information • Allow access a large study population	• Collecting comorbidity information is not primary purpose of claims data • Variable quality of data across different clinical settings (i.e. inpatient vs. outpatient)	Deyo adaptation of the Charlson Comorbidity Index[17], Elixhauser Index[33]

Table 1 Merits of Analytic Strategies for Comorbidity Measurement

	Charlson Comorbidity index[20]	Elixhauser Index[33]	RxRisk[176]		HRQL comorbidity index[41]	
Items	Myocardial infarct, Congestive heart failure, Peripheral vascular disease, Cerebrovascular disease, Dementia, Chronic pulmonary disease, Connective tissue disease, Ulcer disease, Stroke or transient ischemic attack, Diabetes, Hemiplegia, Moderate or severe renal disease, Diabetes with end organ damage, Any tumor, Leukemia, Lymphoma,	Congestive heart failure, Cardiac arrhythmias, Valvular disease, Pulmonary circulation disorders, Peripheral vascular disorders, Hypertension, Paralysis, other neurological disorders, Chronic pulmonary disease, Diabetes, uncomplicated, Diabetes, complicated, Hypothyroidism, Renal failure, Liver disease, Peptic ulcer disease excluding bleeding, AIDS,	**RxRisk Class** (Example)[1]	**Representative Drug Class(es)** (Example)	**For physical aspect of HRQOL:** Paralysis, Rheumatoid arthritis and rheumatic disorders, Heart failure, Systematic Lupus erythematosus, Ischemic heart disease, Osteoarthritis/ nontraumatic joint disorders, Hepatitis, Diabetes, Degenerative neurologic disorders, Peripheral and central vascular diseases, Spinal column disorders, Obstructive pulmonary disease, Gastric and	**For mental aspect of HRQOL:** Affective disorders, schizophrenia, and other psychoses, Anxiety and depression, HIV infection, Epilepsy and convulsions, Hepatitis, Systemic lupus erythematosus , Heart failure, Headaches, Biliary and liver disorders, Anemia, Gastric and duodenal ulcer, Degenerative neurologic disorders, Diabetes, Asthma, Spinal column disorders
			Acne, pediatric	Anti-acne peroxides, anti-acne tretinoin ,retinoid, topical macrolides,		
			Allergic rhinitis, pediatric	Anti-inflammatory glucocorticoids		
			Amino acid disorder, pediatric	Amino acids,		
			Anxiety and tension, adult	Salicylate combinations, barbiturates, benzodiazepines, meprobamate, miscellaneous hypnotics, paraldehyde,		

	Moderate or severe liver disease, Metastatic solid tumor, AIDS	Lymphoma, Metastatic cancer, Solid tumor without metastasis, Rheumatoid arthritis/collagen vascular diseases, Coagulopathy, Obesity, Weight loss, Fluid and electrolyte disorders, Blood loss anemia, Deficiency anemia, Alcohol abuse, Drug abuse, Psychoses, Depression			duodenal ulcer, Hypertension, Asthma, Arrhythmias, Esophageal disorders, Thyroid disorders	

HRQL: Health-related Quality of Life, AIDS: Acquired immune deficiency syndrome; 1: complete drug classification of the RxRisk in Appendix 1

Table 2 Content of Selected Comorbidity Measures

Index	Items	Weights	Final score	Adaptations	Health Outcome of Interest in Targeted Population (n=no.)
Charlson Comorbidity index[20]	19 comorbid conditions	0-RR 1.2-1.5 1-RR 1.5-2.5 2-RR 2.5-3.5 3-RR 3.5-4.5 6-RR>6	Sum of weights assigned to present conditions	-ICD-9[17] -Age[156] -Patients with amputations [178] Questionnaire [15]	In-hospital mortality in ICU patients (n=206)[154]; Post-discharge all-cause mortality in breast cancer (n=685)[20] and patients with hypertension or diabetes (n=226)[156]; Physical functional outcome in lower limb amputees (n=24)[178]; Healthcare costs in enrollees in the HMO (n=20,378)[157]; HRQOL in adults aged≧18 (n=12,812)[41]
Elixhauser Index[33]	30 comorbid conditions	Empirical estimation: regression parameter estimates for each comorbid condition [175]	Sum of weights assigned to present conditions	-ICD-9	In-hospital mortality in MI (n=4,833)[37], CHF (n=56,735) [38], COPD (n=34,175)[38], HTN (n=22,710)[38], ACVD (n=52,281)[38]; Healthcare costs in enrollees in the HMO (n=20,378)[157]; Healthcare utilization in osteoarthritis (n=306)[174]
RxRisk [176]	36 comorbid conditions, represented by corresponding medication class	Empirical estimation: regression parameter estimates for sex, age group, and	Sum of weights assigned to present conditions, which are indicated by	-ICD-9	Total healthcare costs, ambulatory care costs and primary care visits in children aged < 18 (n=81,119)[179] and enrollees in the HMO (n=106, 245),[176] Total healthcare costs in Veterans Health Administration

		each of the comorbid condition indicated by drug use[177]	the occurrence of medication use		population (n=76,772),[173]
HRQL comorbidity index[41]	20 and 15 comorbid conditions for physical and mental functions of health outcomes, respectively	Physical health: 1: β <3.5 2: β 3.5 -10, 3: β >10 Mental health: 1: β <2, 2: β 2-5 3: β >5	Sum of weights assigned to present conditions	-ICD-9	HRQOL in adults aged greater than or equal to 18 years (n=12,812)[41]

HMO: Health Managed Organization, MI: myocardial infarction, CHF: congestive heart failure, COPD: Chronic obstructive pulmonary disease; HTN = Hypertension with complications; ACVD = acute cerebrovascular disease, HRQOL: Health related quality of life

Table 3 Comparisons of Selected Comorbidity Measures

2.1.4. Issues and Challenges in Comorbidity Research

In reviewing previous comorbidity research, there appear several issues and challenges regarding comorbidity scoring systems and their use. In the following section, we summarize these important issues and potential further enhancements in the measurement of and adjustment for comorbidity, which would lead to improved internal validity of similar analyses.

First, the lack of consensus regarding the definition of comorbidity is of special concern and may explain some of the variability in previous comorbidity research findings. Particularly, two terms, comorbidity and multimorbidity, often seem to be used interchangeably in the literature. However, by definition, for research on multimorbidity no index disease is used, whereas for comorbidity research an index disease is obligatory. The selection of appropriate measures in part depends on whether the focus in on measuring the total burden of diseases in a patient (generic multimorbidity measures) or the burden of comorbid diseases in addition to the condition of interest (generic comorbidity measures) In the later case, the index disease is omitted from the comorbidity measurement.

Second, regarding chronology of comorbid conditions, two issues need to be specified when collecting comorbidity information, including the time span in which to assess comorbid conditions and the sequential relationship between an index disease and comorbid condition. Particularly, in order to obtain the accuracy of comorbidity information, according to the presence of comorbid condition at the time of clinical decision making, it is important to distinguish between prior, coexistent, and subsequent comorbid conditions and complications, in the relation to an index disease.

Third, several typologies of comorbidities have been classified, which represent possible ways of defining comorbid conditions, instead of common approaches that are either based on a simple counts of diagnoses or other uni-dimensional scores as a means of capturing the effect of comorbidity on health related outcomes [61]. Although these typological approaches could provide more

insightful information to clinicians and researchers, little research has been on one of these approaches.

Distinguishing comorbidities based on these typologies, such as concordant versus discordant conditions and symptomatic versus asymptomatic conditions, has been given increasing attention by researchers. Studies have shown that an increased likelihood of guideline-consistent management specific to an index disease for patients with more concordant conditions was associated with lower physician's adherence to treatment guideline specific to an index disease [180-184]. Also, recent studies show that patients are often less likely to forego treatment for asymptomatic conditions, such as diabetes and hypertension than treatments aimed mainly at symptom relief, such as analgesics. This evidence suggests that different types of comorbidities may place differential effects in health related behaviors and outcomes. Therefore, disentangling the effects of comorbidities based on typologies of comorbidities deserve further research consideration, in order to better manage the consequences of comorbidities.

Fourth, it has been recognized that knowledge regarding the causes of comorbidity between disorders has a significant impact on research regarding the classification, treatment, and etiology of the disorders [185]. Although previous research have proposed comprehensive sets of possible relationships for the comorbidity between disorders [186], the validity of these etiologic models were only assessed in simulation studies [185]. Further research can be based on other approaches, such as using longitudinal data, to test specific comorbidity models. Knowledge regarding the etiology of comorbidity between disorders could provide insights about the relationships between comorbidities. For example, two comorbid conditions resulting from the same cause may be related to each other. Also, it is possible that one disorder causes another disorder, which can be called concordant comorbidity. So, the understanding of etiology of comorbidities could assist identifying potential interactions or any mechanisms between comorbidities, which is commonly ignored by comorbidity measures that sum all selected comorbid conditions to represent one's comorbidity. These summed scores implicitly assume that there are only additive relationships among comorbidities. The knowledge of

the etiology of comorbidities can be applied to develop effective prevention intervention related to comorbidities, which could possibly curb the growing demands for health care due to increasing prevalence of comorbidities.

Lastly, because there is no gold standard comorbidity measure, the selection of alternative measures in part depends on target disease population (index disease group) and health related outcome(s) of interest [187, 188]. Also, the availability of data sources for constructing comorbidity index (i.e., medical records, claims and self-report) and the strategies for examining a comorbidity score as a mean of capturing comorbidities (i.e., a simple sum of presence conditions, a weighted sum of conditions) need to be considered. Specifically, the choice among alternative comorbidity measures needs to take into account advantages and disadvantages of each type of data sources and analytic strategies for constructing comorbidity index and score.

2.2. Type 2 Diabetes

The following section will provide an overview of the literature related to the prevalence of type 2 diabetes, recommended treatments to type 2 diabetes, medication related adherence in type 2 diabetes, economic impact of diabetes, and healthcare resource utilization by type 2 diabetes patients.

2.2.1 Prevalence of Type 2 Diabetes

The prevalence of diagnosed diabetes in individuals aged ≥20 years rose significantly from 5.1% in 1988-1994 to 7.7% in 2005-2006 (p=.0001) in the US population; this increases was significant after accounting for differences in age and sex distributions between two surveys (p=.0002) [189]. An estimated 11.5 million US adults currently have type 2 diabetes (age-adjusted prevalence of 7.1%), according to the National Health and Nutrition Examination Surveys (NHANES) 1999-2004. This is a significant increase from 5.8%, or 8.0 million adults, during 1988-1994 (NHANES III) (p=.001).

Regarding age-specific prevalence rates, persons aged 30-54 had significantly higher prevalence in 1999-2004 (3.8%) as compared to 1988-1994 (2.6%, p=.002), as did adults aged 65-74 years (15.6% vs. 11.2%, p=.010). Although prevalence of type 2 diabetes did not increase in women, an increase in men was evident for 1999-2004 (7.6%) compared to 1988-1994 (5.5%, p<.001) [190]. Also, the prevalence rate of comorbid conditions increases with age. It has been shown that patients with higher comorbidity, as measured by the CDS, tended to be older [191]. Because the proportion of the U.S. population aged 65 and older is projected to increased dramatically, the elderly population with type 2 diabetes and the associated burden of comorbidity can be expected to grow.

Diabetes is not only a chronic devastating disease which causes high rates of death directly as the evidence of 9% of the global mortality related to diabetes corresponding to four million deaths per year, but also a strong places patients at high risk of heart disease, blindness, kidney failure, extremity amputations, and other medical or comorbid conditions [50, 51]. During 1999-2004, 86 % of persons

treated for type 2 diabetes had at least one comorbid condition of interest; 21% had all three comorbid conditions. Most of them suffered from hypertension, hyperlipidemia, and/or obesity, and glycemic control rates were lowest for those with all three conditions [190]. In fact, among five prevalent disease populations in the US, including mood disorders (depressive and manic-depressive disorders), diabetes, heart disease, hypertension, and asthma, the prevalence rate of patients with at least one comorbid condition is high in diabetes patients, particularly compared to hypertension patients ($p<.001$ diabetes compared with hypertension patients) [52].

2.2.2 Medical Resource Use and Expenditure Attributed to Type 2 Diabetes

Comorbidity among patients with diabetes is associated with considerable consequences for health care use and related costs [2, 8, 192-201]. Comorbidity has been shown to intensify health care utilization and to increase medical care costs among patients with diabetes.

Regarding institutional care, of the projected 186 million days (22%) that are incurred by people with diabetes, 24.3 million (13%) are attributed to diabetes. While 1 in 4 nursing facility days is incurred by a person with diabetes, 1 in 10 days is attributed to diabetes. For outpatient care, about half of all physician office visits, emergency visits, hospital outpatient visits, and outpatient prescriptions (excluding oral agents and insulin) incurred by people with diabetes are attributed to their diabetes [201].

When considering contributions of comorbidities in healthcare resource use in this population, a strong correlation has been found between comorbidity and the use of hospital care (i.e., hospital admission)[2, 195, 196, 200], general practitioner (GP) care [200], and ambulatory specialist care [200]. Conversely, patients without comorbidity were found to use little care [200]. Moreover, both diabetes-related (concurrent) and non-diabetes-related (discordant) comorbidities increase the use of medical care substantially in patients with diabetes. This suggests that non-diabetes-related comorbidities are as important utilization drivers as diabetes-

related comorbidities [200]. Also, the large impact on health care utilization of patients with diabetes occurs when diabetes is included in a constellation of concurrent and discordant comorbidities [200].

Furthermore, differences in health care utilization patterns were observed between the comorbidities. Diabetic foot results in a large increase in the use of GP care, but not in the use of medical specialist care and hospital care. Coronary heart diseases, stroke, depression, musculoskeletal diseases and cancer result in a substantially increase in both GP care, medical specialist care and hospital care [200]. However, with consistent finding across studies [145, 200, 202], the average of stay in the hospital increases in most comorbidities.

When healthcare expenditures are examined, approximately $205 billion in expenditures are incurred by people with diabetes, reflecting, reflecting $1 every $5 health care dollars. Costs attributed[4] to diabetes total $116 billion, or 57% of total medical costs incurred by people with diabetes, reflecting over $1 of every $10 health care dollars attributed to diabetes. Almost half of all health care expenditures attributed to diabetes come from higher rates of hospital admission and longer average lengths of stay per admission. Of the projected $430 billion in national expenditures for hospital inpatient care (including both facility and professional services costs), approximately $97 billion (or 23%) is incurred by people who have diabetes and $53 billion (14%) is directly attributed to their diabetes. Among outpatient care services, retail prescriptions (excluding insulin and oral agents) are another major expense category, with 17% of prescription costs incurred by people with diabetes and 8% of costs ($12.7 billion) attributed to their diabetes [201].

In this population, management of medical conditions, which are not directly attributed by diabetes (or called discordant comorbidities of diabetes), accounted for approximately 76% of the projected $340 billion in the U.S. national expenditures for hospital inpatient care. The second largest category of diabetes costs is inpatient days associated with cardiovascular diseases, which can be viewed

[4] The term “attributed” to mean the difference in health care use for people with diabetes compared to what their health car use would be in the absence of diabetes-estimating the excess health care use that is theoretically due to (or caused by) diabetes and its complications

as concurrent comorbidities of diabetes. Cardiovascular diseases in the patients with diabetes accounts for $66 billion per year in inpatient expenditures in the U.S. (or 15% of total U.S> medical expenditures for inpatient care.) However, with only 7% of inpatient days for this condition group attributed to diabetes disease itself, comorbidities, particularly discordant conditions, this constitutes the single largest contributor to the attributed medical cost of diabetes. Among concurrent comorbidities in patients with diabetes, cardiovascular diseases contribute major consumption of hospital inpatient care [201]. Also, in this population, as diabetes-related complications or comorbid conditions develop and progress, disease management costs increase [198, 203].

2.2.3 Standards of Medical Care in Type 2 Diabetes

2.2.3.1 Glycemic Control

The American Diabetes Association (ADA) has annually published clinical practice recommendations for diabetes care, including screening, diagnostic, and therapeutic actions that are known or believed to favorably affect health outcomes of patients with diabetes. These standards of care are intended to provide clinicians, patients, researchers, payers, and other interested individuals with the components of diabetes care, treatment goals, and tools to evaluate the quality of care [204].

Controlled clinical trials, such as the Diabetes Control and Complications Trial Research Group (DCCT)[205] and the Stockholm Diabetes Study in type 1 diabetes[206], and the UK Prospective Diabetes Study (UKPDS)[207, 208] and the Kumamoto study [209] in type 2 diabetes, have helped to establish the glycemic goals of therapy that result in improved long-term outcomes. These clinical trials, in concert with epidemiological data [210, 211], support decreasing glycemia as an effective means of reducing long-term microvascular and neuropathic complications.

One primary technique available to assess the effectiveness of the management plan on glycemic control is glycosylated hemoglobin A1c (HbA1c) test[204]. Because A1c is thought to reflect average glycemic over several months[212], and has strong predictive value for diabetes complications[213, 214],

A1c testing should be performed routinely in all patients with diabetes, at initial assessment and then as part of continuing care[204]. The UKPDS demonstrated for each 1% reduction in the mean HbA1c level, there was a 21% risk reduction for any diabetes-related end point, including myocardial infarction, stroke, amputation, and microvascular complications [214].

The glycemic goal recommended by the ADA, selected on the basis of practicality and the projected reduction in complications over time, is, in general, an HbA1c level of <7% [1]. The most recent glycemic goal set by the International Diabetes Federation is an HbA1c level of <6.5%. Several recent clinical trials have aimed for HbA1c levels ≤6.5% with a variety of interventions [215-217]. The results of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, which had the primary objective of decreasing cardiovascular disease (CVD) with interventions aimed at achieving an HbA1c level of <6.0% versus interventions aimed at achieving an HbA1c level of <7–7.9%, showed excess CVD mortality in the intensive treatment group (HbA1c <6.0%) [215]. Results from the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial and the Veterans Affairs Diabetes Trial, both of which had different interventions and study populations than ACCORD, did not demonstrate any excess total or CVD mortality with intensive regimens that achieved HbA1c levels comparable to the 6.5% in ACCORD[216, 217]. However, none of the studies has demonstrated a benefit of intensive glycemic control on their primary CVD outcomes. The most recent consensus from the ADA and the European Association for the Study of Diabetes is that an HbA1c level of ≥7% should serve as a call to action to initiate or change therapy with the goal of achieving an HbA1c level of <7%[218].

It is mindful that this goal is not appropriate or practical for some patients, and clinical judgment based on the potential benefits and risks of a more intensified regimen needs to be applied for every patient[218]. Factors such as life expectancy, risk of hypoglycemia and the presence of CVD need to be considered for every patient before intensifying the therapeutic regimen[218]. Less stringent A1c goals may be appropriate for patients with a history of severe hypoglycemia, patients with limited life expectancies, children, individuals with comorbid conditions, and

those with longstanding diabetes and minimal or stable microvascular complications.[204]

So, although intensive glycemic control has been recognized as key beneficial strategy for diabetes management, its benefits such as reducing the risk of costly and disabling complications associated with diabetes [208, 214] might not be feasible for heterogeneous diabetic patients, particularly for elderly diabetes or those with comorbidities. In a computer-generated decision analysis, Huang et al. modeled the benefit of intensive glycemic control (HbA1c 7.0%) in hypothetical older patients aged 60-80 years with type 2 diabetes mellitus and various life expectancies estimated from a mortality index. Expect benefits of intensive glycemic control ranged from 51-116 additional days of quality-adjusted life expectancy; however, expected benefits declined as the patient's age and the number of comorbidities and functional impairment increased, and increased with duration of type 2 diabetes. One may argue that in this extrapolation of theoretical model the input data such as the UK Prospective Diabetes Study (UKPDS)[208] were several decades old, therefore, interpretation of the mean quality-adjusted days gained lacked comparative benchmarks. Also, a "survivor effect' probably accounted for the increased benefit associated with an increased benefit associated with an increased duration of type 2 diabetes. Nevertheless, the data do suggest that the benefits of intensive glycemia control might be diminished in older patients with multiple comorbidities and functional impairments [219].

Therefore, for any individual patient, the frequency of A1c testing should be dependent on clinical situation, the treatment regimen used, and the judgment of the clinician. The ADA guidelines recommend that the patients with stable glycemia well within target may do well with testing only twice per year, while unstable or highly intensively managed patients (e.g., pregnant type 1 women) may be tested more frequently than every 3 months [204].

2.2.3.2 Quality of Care in Type 2 Diabetes

It is now well evident that a good clinical care and self-care activities can postpone complications and improve the quality of the patient's life. On the other hand, improving the quality of care can result in a significant decrease in diabetes complications cost. Therefore, better management and more efficient use of limited health resources to improve the quality of diabetes care is very important. The Healthcare Effectiveness Data and Information Set (HEDIS) is a tool developed by the National Committee for Quality Assurance (NCQA) [220], which is an independent, not-for-profit organization dedicated to measuring the quality of U.S. health care, to measure performance on several dimensions of care. Health plans has employed the HEDIS measures to report to employer groups and to participate in the NCQA's accreditation processes. The specifications and definitions of the measures are very detailed and refined regularly, making the HEDIS measures a consistent and reliable way to compare quality of care in different groups [221].

The HEDIS has developed quality indicators for evaluating comprehensive diabetes care [222], which include several important features of effective, multiphase management of diabetes and its complications. These measures estimated the percentage of health plan members 18-75 years of age with diabetes (type 1 and type 2) who had each of the following: (1) had a HbA1c test; (2) had poorly controlled HbA1c (level greater than 9%); (3) HbA1c control (<8%) (first-year indicator); (4) had a serum cholesterol level (LDL-C) screening; (5) had their LDL-C level controlled to less than 100 mg/dl; (6) had an eye exam (retinal) performed; (7) blood pressure control (<130/80 mmHg).

The results of recent studies have suggested that having multiple morbidities results in poorer quality of care as the result of competing demands for physician attention[81, 223], multiple overlapping guidelines[224], and increased risk of adverse drug events[225]. It has been cautioned that standard care for a given disease may be contradictory to treatments for other comorbid diseases. However, currently few disease specific treatment guidelines have been developed in the context of comorbid conditions. In part because patients with multiple comorbid conditions have often been excluded from the evidence-generating randomized controlled trials that from the basis for treatment guidelines on a specific disease,

most disease specific practice guidelines today, such as diabetes disease managements, are entirely focused on diabetes itself and do not address the challenges to patients and providers of managing concomitant conditions.

Also, given current growing enthusiasm for "pay for performance" era, physicians may feel pressure to adopt a "one size fits all" approach and order tests to improve their performance on quality indicators developed from trials that excluded patients with multiple comorbid conditions. Two recent articles, one by Boyd and colleagues[5][226] and the other by Tinetti and colleagues[6][224], used hypothetical patients to consider possible concerns with applying current guidelines to patients with multiple comorbid conditions. Both manuscripts concluded that guidelines concordant care may result in great expense and marginal benefits, and cautioned that enforcing quality measurement for patient with complex comorbid conditions may result in unintended harm unless future quality measures takes a broader view of patient' coexisting medical conditions and preferences.

Therefore, despite the support that disease-specific guidelines give, such guidelines are likely to introduce more problems than they solve when used in patients with comorbidity. Treatment or even diagnosis of a disease might interact negatively with the treatment or natural course of a co-existing disease[227]. For example, in chronic obstructive pulmonary disease, state-of-the-art treatments might include oral corticosteroids, but if the patient also has diabetes mellitus, oral corticosteroids might not be in the patient's best interests. Promotion of physical activity- which would be beneficial for chronic obstructive pulmonary disease- might not be possible if there is severe osteoarthritis of the hip. Conversely, hip replacement, indicated by the severity of the osteoarthritis, will be contraindicated if a patient's pulmonary capacity precludes major anesthesia. These examples show why performance indicators based on single-disease guidelines cannot accurately

[5] In Boyd et al's study, application of available major guidelines to an illustrative case of a woman with five conditions (hypertension, chronic obstructive pulmonary disease, diabetes, osteoarthritis, and osteoporosis) resulted in the theoretical need for multiple daily medications, complex instructions, and monthly medication costs exceeding $400.

[6] In Tinetti et al's study, a hypothetical older woman with hypertension, coronary artery disease, depression, diabetes, and osteoporosis would need to take as many as 11 medications, with the potential for decreasing marginal benefit and increasing adverse drug event risk.

reflect the quality of care with multiple chronic diseases. Dealing with comorbidity needs a patient-centered rather than a disease-oriented approach. Addressing individual needs while integrating various disease perspectives is at the root of general practice and determines its effectiveness[228].

In fact, the categorization of comorbidities implicitly provides an avenue to develop disease specific management guidelines which account for patients with multiple chronic diseases. Four general categories of comorbidities have appeared in the literature[4, 61]: causal, diseases with a common pathophysiology; complicating, disease-specific complicating morbidity; concurrent, co-existing chronic morbidity without any known causal relation to the index disease; and intercurrent, referring to interacting acute illness, usually limited in time.

When the comorbidity is causally related to or is a complication of the index disease, disease-specific guidelines can be used to direct management. However, these guidelines must include information on the full spectrum of health risks associated with the index condition. Such guidelines would enhance proactive management of illness, but their development will require patients with a mix of comorbid conditions to be included in randomized trials[229].

The problems with disease-specific guidelines come to the fore when there is concurrent morbidity, particularly in ageing-related diseases when comorbidity is linked to frailty[230]. The interacting effects of diseases and their management require more complex and individualized care than simply the sum of separate guideline components. And it is only to a limited extent possible to account for this in the framework of guidelines, where statements on management are by definition directed at subgroups. Instead of advocating the development of new guidelines taking all possible combinations of diseases into account, a holistic patient-centered approach, ensuring continuity of care and integrating the patients biopsychosocial domains need to be emphasized[231].

Meduru et al have examined the impact of different types of comorbidities in glycemic control using a summary comorbidity score to capture whole comorbidity conditions [232]. They argued that the CCI, the most common adjustment for physical comorbidity [233-237], and other measures, including the presence of

diabetes-related complications and simple count of comorbid conditions [237-239], may not adequately control for chronic illness with complexity that may influence glycemic control; summary scores like the CCI do not provide insight into comorbidities that may have varying associations with glycemic control [232].

In this regard, they used the recent conceptual model of comorbid chronic illness complexity in diabetes care by Piette and Kerr as a starting point and operationalized comorbid conditions into three domains of complexity[61]: (1) diabetes- related conditions, called *concordant* conditions, (2) non-diabetes related conditions, called *discordant* conditions, (3) mental illness and substance abuse conditions.

Their study results demonstrated that the association between comorbidity and optimal glycemic control varied by the type of comorbidities. This is, patients with *discordant* conditions or mental illness/substance abuse were more likely to have HbA1c<7%, while those with *concordant* conditions were less likely to have HbA1c<7%. Also, another noteworthy finding is that the associations between comorbidity and glycemic control vary by HbA1c threshold. Both discordant conditions and mental illnesses/substance abuse were more strongly associated with HbA1c<7% than HbA1c<8%. The varying associations of comorbidity categories with optimal glycemic control have implications for the validity of using HbA1c<7% threshold as a performance measure for diabetes quality of care. When using HbA1c<7% as a performance measure, appropriate risk adjustment based on comorbidity may be necessary. In the absence of validated and widely accepted risk adjustment model, the study findings highlighted the need for developing appropriate risk adjustment models for optimal glycemic control [232].

2.2.3.3 Standard Treatments for Type 2 Diabetes

The ADA and the European Association for the Study of Diabetes recently has published an updated consensus statement on the approach to management of hyperglycemia in individuals with type 2 diabetes [218]. The consensus specifies a treatment algorithm with four highlights: (1) achievement and maintenance of near

normoglycemia (HbA1c <7.0%), (2) initial therapy with lifestyle intervention and metformin (MET), (3) rapid addition of medications, and transition to new regimens, when target glycemic goals are not achieved or sustained, (4) early addition of insulin therapy in patients who do not meet target goals. The overall objective is to achieve and maintain HbA1c levels of <7% and to change interventions at as rapid a pace as titration of medications allows when target glycemic goals are not being achieved.

The treatment algorithm (table 4) takes into account the evidence for A1c-lowering of the individual interventions, their synergies, and their expense. The judgments and comparisons of blood glucose-lowering medications, and combinations of such agents, were primarily on the basis of their capacity to decrease and maintain HbA1c levels and according to their safety, specific side effects, tolerability, ease-of-use and expense [218].

Intervention	Expected decrease in HbA1c (%) with monotherapy	Advantages	Disadvantages
Tier 1: well-validated core			
Step 1: initial therapy			
Lifestyle to decrease weight and increase activity	1.0-2.0	Broad benefits	Insufficient for most within first year
Metformin	1.0-2.0	Weight neutral	GI side effects, contraindicated with renal insufficiency
Step 2: additional therapy			
Insulin		No dose limit, rapidly effective, improved lipid profile	One to four injections daily, monitoring, weight gain, hypoglycemia, analogues are expensive
Sulfonylurea	1.0-2.0	Rapidly effective	Weight gain, hypoglycemia(especially with glibenclamide or chlorpropamide)
Tier 2: less well-validated			
Thiazolidinedione	0.5-1.4%	Improved lipid profile (pioglitazone), potential decrease in MI (pioglitazone)	Fluid retention, CHF, weight gain, bone fractures, expensive, potential increase in MI (rosiglitazone)
GLP-1 agonist	0.5-1.0	Weight loss	Two injections daily, frequent GI side effects, long-term safety not established, expensive
Other therapy			
α-Glucosidase inhibitor	0.5-0.8	Weight neutral	Frequent GI side effects, three times/day dosing, expensive
Glinide	0.5-1.5*	Rapidly effective	Weight gain, three times/day dosing, hypoglycemia, expensive
Pramlintide	0.5-1.0	Weight loss	Three injections daily, frequent GI side effects, long-term safety not

			established, expensive
DPP-4 inbitor	0.5-0.8	Weight neutral	Long-term safety not established, expensive

* Repaglinide more effective in lowering HbA1c than nateglinide; CHF, congestive heart failure; GI, gastrointestinal; MI, myocardial infarction

Table 4 Summary of Glucose-Lower Interventions

Source: [218]

Lifestyle interventions

The major environmental factors that increase the risk of type 2 diabetes are over-nutrition and a sedentary lifestyle, with consequent overweight and obesity [240, 241]. Interventions that reverse or improve these factors have been demonstrated to have a beneficial effect on control of glycemia in established type 2 diabetes [242]. The most convincing long-term data indicating that weight loss effectively lowers glycemia have generated in the follow-up of type 2 diabetic patients who have had bariatric surgery. In this setting, with a mean sustained weight loss of > 20 kg, diabetes is virtually eliminated [243-246]. Weight loss of as little as 4 kg will often ameliorate hyperglycemia[218]. Additionally, weight loss and exercise improve coincident CVD risk factors, such as blood pressure and atherogentic lipid profiles, and ameliorate other consequences of obesity [242, 247, 248]. Given these beneficial effects, which are usually seen rapidly-within weeks to months-and often before there has been substantial weight lost, a lifestyle intervention program to promote weight loss and increase activity levels should, with rare exceptions, be included as part of diabetes management [218]. However, the limited long-term success of lifestyle programs to maintain glycemic goals in patients with type 2 diabetes suggests that the large majority of patients will require the addition of medications over the course of their diabetes [218].

Medications

The characteristics of currently recommended glucose-lowering medications, when used as monotherapy, are summarized in Table 4. The glucose-lowering effectiveness of individual therapies and combinations demonstrated in clinical trials is predicated not only on the intrinsic characteristics of individual drug, but also on the duration of diabetes, baseline glycemia, previous therapy and other factors. A major factor in selecting a class of drugs, or a specific medication within a class, to initiate therapy or when changing therapy, is the ambient level of glycemic control. When levels of glycemia are high (e.g. HbA1c>8.5%), classes with greater

and more rapid glucose-lowering effectiveness, or potentially earlier initiation of combination therapy, are recommended; however, patients with recent-onset diabetes often respond adequately to less intensive interventions than those with longer term disease[249]. When glycemic levels are closer to the target levels (e.g. HbA1c<7.5%), medications with lesser potential to lower glycemia and/or a slower onset of action may be considered.

The choice of glycemic goals and the medications used to achieve them must be individualized for each patient, balancing the potential for lowering HbA1c and anticipated long-term benefit with specific safety issues, as well as other characteristics of regimens, including side effects, tolerability, ease-of-use, long-term adherence, expense and the non-glycaemic effects of the medications. When the disease is progressing as characterized by worsening glycemia, higher doses and additional medications are required over time if treatment goals are to be met [218].

Metformin (MET)

MET is the only biguanide available in most of the world. Its major effect is to decrease hepatic glucose output and lower fasting glycemia. Typically, MET monotherapy will lower A1c levels by ~ 1.5 percentage points [250, 251]. It is generally well tolerated, with the most adverse effects being gastrointestinal. MET monotherapy is not usually accompanied by hypoglycemia and has been used safely, without causing hypoglycemia, in patients with pre-diabetic hyperglycemia [213]. The major nonglycemic effect of MET is either weight stability or modest weight loss, in contrast with many of the other blood glucose-lowering medications. Renal dysfunction is considered a contraindication to MET use because it may increase the risk of lactic acidosis, an extremely rare (less than 1 case per 100,000 treated patients) but potentially fatal complication [252], particularly for patients with estimated glomerular filtration rate falls to <30 ml/min [253].

Sulfonylureas (SUs)

The SU class agents lower glycemia by enhancing insulin secretion. Like MET, SUs will lower A1c levels by ~1.5 percentage points[251, 254]. Although the onset of the glucose lowering effect of SU monotherapy is relatively rapid compared with, for example, the thiazolidinediones (TZDs), maintenance of glycemic targets over time is not as good as monotherapy with a TZD or MET [255].

The major adverse side effect is hypoglycemia, which can be prolonged and life-threatening, but such episodes, characterized by a need for assistance, coma or seizure, are infrequent. However, severe episodes are relatively more frequent in the elderly. Chlorpropamide and glibenclamide (known as glyburide in the USA and Canada), are associated with a substantially greater risk of hypoglycemia than other second-generation SUs (gliclazide, glimepiride, glipizide, and their extended formulations), which are preferable (Table 4) [256, 257]. SU therapy was implicated as a potential cause of increased CVD mortality in the University Group Diabetes Program (UGDP) study[258]. Concerns raised by the UGDP that SUs, as a drug class, may increase CVD mortality in type 2 diabetes were not substantiated by the UKPDS or ADVANCE study [208, 217]. Additionally, weight gain of ~2 kg is common following the initiation of SU therapy [218]. The glycemic benefits of SUs are nearly fully realized at half-maximal doses and higher doses should generally be avoided[218].

Thiazolidinediones (TZDs)

TZDs or glitazones are peroxisome proliferator-activated receptor γ modulators; they increase the sensitivity of muscle, fat and liver to endogenous and exogenous insulin ('insulin sensitizers') [259]. The data regarding the blood glucose lowering effectiveness of TZDs when used as monotherapy have demonstrated a 0.5–1.4 percentage point decrease in HbA1c. The TZDs appear to have a more durable effect on glycemic control, particularly compared with SUs [259].

The most common adverse effects with TZDs are weight gain and fluid retention, with peripheral edema and a twofold increased risk for congestive heart failure [260, 261]. There is an increase in adiposity, largely subcutaneous, with

some reduction in visceral fat shown in some studies. The TZDs either have a beneficial (pioglitazone) or neutral (rosiglitazone) effect on atherogentic lipid profiles [262, 263].

Pioglitazone was associated with a 16% reduction in death, myocardial infarction and stroke—a controversial secondary endpoint reported to have marginal statistical significance [264]. Meta-analyses have supported a possible beneficial effect of pioglitazone on CVD risk[265]. Although the data are less than conclusive for a CVD risk with rosiglitazone or a CVD benefit with pioglitazone, it has been cautioned[266] in using either TZD, on the basis that they are both associated with increased risks of fluid retention and congestive heart failure, and an increased incidence of fractures in women, and perhaps in men[252, 260, 261, 267].

Although the meta-analyses discussed above are not conclusive regarding the potential cardiovascular risk associated with rosiglitazone, given that other options are now recommended, the consensus group members unanimously advised against using rosiglitazone. Currently, in the USA, the TZDs are approved for use in combination with MET, SUs, glinides and insulin.

2.2.4 Healthcare Providers' Adherence to Diabetes Specific Guideline in Diabetic Patients with Comorbidities

It has been recognized that multiple medical conditions can place competing demands for physicians' attention [81, 223], and, therefore, affect their adherence to treatment guidelines and quality of care. However, to date, there is little research on the relationship of comorbidities and physician treatment adherence. Also, among limited evidence regarding the impact of comorbidities on physician's behavior, there appeared to be inconsistent study findings.

Research has shown that diabetic patients with more comorbid conditions are more likely to receive recommended care. For example, it has been found that one unit increase in the severity of comorbidities measured by the CCI was associated with 3% increased odds of having at least one LDL-c testing (95% CI: 1.00-

1.05).[268] The percentage of diabetic patients with more than 5 comorbidities reaching blood pressure and cholesterol targets exceeded normal predictions during the first two years of pay for performance (by 3.1% (95% CI: 1.1-5.1) for BP and 4.1% (95% CI 2.2-6.0) for cholesterol. The percentage of patients meeting the HbA1c target in the first two years of this program was significantly lower than normal predictions in all patients, with the greatest shortfall in patients without comorbidity (3.8%, (95% CI: 2.6-5.0))[269]. More recently, Clark et al's study showed that the among Medicaid beneficiaries, patients with type 2 diabetes and higher overall illness burden as measured by the Chronic Illness and Disability Payment System (CDPS)[7] had higher quality of diabetes care than those with low illness burden, particularly in the HbA1c testing and nephropathy monitoring [270].

There are several potential explanations regarding such a positive relationship between comorbidities and physician guideline compliance. First, patients with multiple conditions might receive a greater number of clinic invitations, have more frequent attendance and enhanced management as they will be on multiple diseases registers. Second, under the reward structure of pay for performance, it is highly beneficial for practitioners to improve care and control risk factors in patients with several incentivized conditions. For example, achieving good blood pressure control in one patient may contribute to the achievement of treatment targets for hypertension, diabetes and coronary heart disease.

However, on the other hand, patients having multiple conditions may create considerable management complexity, forcing the clinician to consider and prioritize a large array of recommended care, possibly replacing valuable time in the office visit that could be spent addressing issues which have a greater impact on patient health outcomes, therefore, physicians may have a difficulty to be adherent to disease-specific treatment guidelines when treating patients with multiple comorbid conditions[226]. Research has been shown that the quality of care

[7] The CDPS is used to measure the overall burden of illness, a concept that combines the number and relative severity of medical conditions.The CDPS creates an individual-level measure of relative illness burden based on International Classification of Disease, ninth edition (ICD-9) diagnoses, demographic characteristics, and program enrollment type.

indicators, such as routine HbA1c and lipid tests, were lower in the diabetic population with higher comorbidity [271].

These inconsistent findings were all based on a simple summative comorbidity score as a proxy for individual comorbid conditions. In order to examine the differential impact of comorbidities, there is a need to disentangle the effects of different types of comorbidities. Piette and Kerr's conceptualization of typologies of comorbidities has provided an essential framework for studying how comorbidities of different characteristics, such as concordant versus discordant conditions, might affect adherence with guideline-recommended care and with patient self-care recommendations [61].

Piette and Kerr's conceptualization has been empirically supported. Among post-MI patients, both concordance and symptomatic conditions were positively and significantly associated with physician guideline adherence [272]. In a cohort of hypertensive primary care patients, the number of conditions discordant with cardiovascular risk was strongly negatively associated with guideline-consistent hyperlipidemia management even in patients at the highest risk for cardiovascular events and cardiac death [180]. Among patients with stage III colon cancer, those with a CCI score>3 compared with 0 were less likely to be offered recommended chemotherapy (19% compared with 84%) despite such therapy being associated with around a 60% reduction in excess mortality for both all-cause and cancer specific survival in these patients [273].

However, not all studies found that discordant conditions are associated with poorer diabetes care. Desail et al. [274] found that patients with diabetes and comorbid mental disorders were a likely as other diabetic patients to receive foot inspections, retinal exams, and A1c tests. More recently, Dixon et al. [45] found that diabetic patients with schizophrenia had better glycemic control than those without serious mental illness (adjusted mean A1c of 7.7 vs. 9.0%). These studies suggest that the impact of comorbidities may have less to do with concordance than with their influence on patients' exposure to health system supports. Even discordant conditions may increase the overall number of outpatient contacts and, as a result, opportunities for diabetes-related health monitoring and counseling may be greater.

Therefore, based on previous research findings, three possible phenomena have been associated with the impact of comorbidity regarding the impact of comorbidity on physician's adherence to diabetes treatment standards: (1) as the number of comorbidities increase, physicians are forced to forgoing diabetes specific routine standard care, such as HbA1c testing; (2) as the number of comorbidities increases, patients may have more contact with health care system, closer monitoring and better care coordination so recommended care, such as blood pressure testing, are more likely to be prescribed, (3) regardless of increased comorbidities, diabetes specific standard care is invariant among diabetes patients with varying comorbidity due to lack of diabetes care clinical guidelines in the context of comorbid conditions [271]. The theory that different types of comorbidities have varying impacts on diabetes specific management has empirically been supported; however, some studies have reported the positive impact of separately concordant conditions on the diabetes management, whereas others have found negative impacts of individual discordant comorbidities on the diabetes management [61].

2.2.5 Medication Taking Behavior in Type 2 Diabetes

2.2.5.1 Medication Taking Behavior in Type 2 Diabetes

With the expanding armamentarium of diabetes medications over the past decade, multiple pathophysiologic processes can be modified, therapy can be tailored to a person, and alternatives can be provided when adverse effects occur. Pharmacologic therapies for diabetes mellitus, which provide needed physiologic support for insulin deficiency or for insulin resistance, can facilitate excellent control, with the potential for normalization of HbA1c of 0.5% to 2% for oral antidiabetic (OAD) medications and of 1.5%-3.5% for insulin therapy [218], thus increasing the likelihood of attaining good glycemic control while decreasing the risk of diabetic complications.

Moreover, according the ADA, in the years 2004-2006, 57% of diabetic patients (type 1 and type 2) were treated with OAD medications, whereas 14% and

13% were treated with insulin only and a combination of insulin and OAD medication, respectively [275]. The OAD medications assume prominence in antidiabetic treatment.

2.2.5.2 Consequences of Poor Medication Taking Behavior in Type 2 Diabetes

Despite the past decade having seen the development of many simple and effective drug therapies for diabetes, their clinical impact has been limited by poor rates of adherence to diabetes medicines (36% to 93%) [276]. However, fewer patients using insulin report poor adherence [277-285]. In fact, non-adherence to OAD medication may partly explain why only 43% of patients with diabetes mellitus have HbA1c below the 7% level [286, 287] recommended by the American Diabetes Association [204].

Adherence refers to the extent to which a person's behavior (in terms of taking medications, following prescribed medication regimen and a diet, and/or executing lifestyle changes) coincides with advice/recommendations from health care professionals [288]. Medication adherence is a critical self-care activity that has been associated with positive diabetes outcomes, including enhanced blood glucose control [289-294], having fewer hospitalizations [295] and lower health-care costs [170, 296, 297], and possibly reduced mortality [290].

Studies of adherence in diabetes have focused on its glycemic control, its economic burden [298-300], its complications [207, 214] and the cost-effectiveness of antidiabetic drugs [301-306].

One recent study in a managed care setting found that adherence[8] was higher among patients achieving glycemic control, and an inverse relationship was found between OAD medication adherence and HbA1c. Controlling for baseline HbA1c and therapy regimen, each 10% increase in OAD medication adherence was associated with a 0.1% HbA1c decrease [289]. Also, one study showed that a 10% increase in non-adherence to MET was associated with an increase in HbA1c of

[8] based on at least two fills f the index OAD, which is the date of the first OAD prescription fill and defined as the sum of the days supply from the index prescription date to the last fill date (excluding days supply that was dispensed at the final prescription fill), divided by the duration of therapy

0.14% [293]. In a study assessing adherence to DM medications in 301 patients, good adherence[9] was associated with a 10% reduction in HbA1c (p=.0003) [292]. Maier and colleagues evaluated the use of a pocket-size tablet-dispensing device on glycemic control and observed that those using the dispenser had a significant reduction in HbA1c (–0.74 vs. –0.53, $P < .0001$) [307].

In another study of 57,687 diabetic patients in an HMO, those with increased OAD medication adherence according to claims data analyses had fewer emergency department visits, fewer inpatient admissions, and decreased medical care costs [297]. In a recent retrospective cohort (N = 11 532) analysis by Ho and colleagues, 62 diabetic patients who were not adherent (prevalence of 21.3% based on <80% proportion of days covered for OAD, antihypertensives, and statin medications combined) had higher all cause hospitalization ($P < .001$) and all-cause mortality ($P < .001$) than did those who were adherent (>80% PDC) [290].

Low medication possession ratios (MPRs), which are an indicator of poor medication adherence, were generally associated with higher costs among patients with Diabetes Mellitus. For example, one study reported an association of MPR of 60% with mean total costs of $8699 [308]. Balkrishnan et al. found that a 10% increase in MPR for an antidiabetic medication was associated with an 8.6% reduction in total annual health care costs [170]. Studies generally reported increments of mean annual costs according to baseline HbA1c values. For example, the mean annual costs for Medicaid patients with baseline HbA1c<8% were $4475, while for those with HbA1c> 10 were $8088 [38].

2.2.5.3. Factors Influencing Medication Taking Behavior in Type 2 Diabetes

Medication taking behavior, which is measured in terms of adherence to medication treatment regimens, can be challenging for the individuals with diabetes because several factors can influence medication taking behavior [280, 309-316]. Odegard and Capoccia have provided a detailed, well-organized summary of the

[9] Determined by a score of 3 or more out of 4 possible points on Morisky self-report medication adherence assessment

literature regarding medication-taking behavior in the diabetes population [317]. Their review covers 36 articles published between 1990 and 2007 that focus on diabetes and measures of medication adherence. Most of the articles (n=21) are retrospective reviews that evaluate historical data in patients using OAD (n=20) and insulin (n=1). The prospective studies (n=7) verify adherence using medication electronic monitoring systems (5/7) or use patient questionnaires (2/7) to evaluate adherence and the impact of depression on adherence. From this literature, one can learn that simple regimens, monotherapy, once-daily, and fixed-dose combination pills improve medication-taking adherence. Problems that adversely affect adherence are medication side effects, the severity of depression, and the patient's lack of belief in the immediate and future benefits of the diabetes drug.

Moreover, this articles further organized these factors into three aspects, including patient-, medication-, and provider or system-related factors (table 5) [280, 309-316]. Diabetes treatment includes the unique challenges that preclude many individuals from starting or remaining adherent to insulin, including fears of disease worsening, hypoglycemia, social stigma, the use of needles, and weight gain, the severity of depression, insufficient knowledge and skill regarding medication use, lack of beliefs or confidence immediate or future benefits of the medications.

Also, depression, as a concurrent disease that frequently occurs with diabetes, has been recognized as causative challenges for medication taking in those with diabetes. A 2005 report identified depression as a significant factor challenging diabetes medication adherence, with diabetic patients concurrent with depressive symptoms were less likely to report and demonstrate good adherence to OAD medication (42% reporting good adherence versus 67% non-depressed, $P = .03$) [314]. Another study showed that the effects of depression on OAD medication nonadherence rate was 24.5% for those with depression and 18.8% for those with no major depression (nonadherence versus adherence: $P < .005$) [315]. Chao et al [318] also reported that greater depressive symptoms were associated with lower adherence to OAD medication.

Moreover, complexity of regimen (number of medications and number of doses per day), cost, and adverse effects of medications can challenge patient's

medication taking [312]. At the same time, the health care system poses a threat to optimal pharmacologic treatment of diabetes, with corresponding challenges that include provider education, costs of therapy, insurance coverage, and adequacy of follow-up with patients [317].

Among these factors, the most commonly cited factors include regimen complexity (e.g., need to split tables, mix products), dosing frequency greater than twice daily, cost, self-confidence, education about the use of the product, depression, and adverse effects or fear of them [317].

Patient factors	Medication factors	Provider or system factors
✓ Fears: disease worsening, hypoglycemia, needles, social stigma, weight gain ✓ Knowledge and skill: education ✓ Self-efficacy ✓ Health beliefs ✓ Depression ✓ Lack of confidence in immediate or future benefits of the medication ✓ Remembering doses and refills	✓ Complexity of regimen (e.g., more than 1 DM drug, splitting tablets, drawing up insulin) ✓ Frequency of dosing (2 or more times daily results in poorer adherence) ✓ Cost ✓ Adverse effects	✓ Fear that patient will not be able to use therapy ✓ Knowledge: medications, use of insulin, monitoring, diabetes treatment ✓ Skill: able to demonstrate proper use of devices ✓ Inadequate educational support ✓ Inadequate follow-up resource

Table 5 Adherence Barriers to Diabetes Mellitus Medication Use
Source: [280, 309-316]

In addition to the factors summarized by Odegard and Capoccia [317], an expanded view that takes into account interactions between the patient and healthcare providers and between the patient and healthcare system have been emphasized to have the greatest effect on improving medication adherence [319, 320]. The interactions among the patient, healthcare provider, and healthcare system depicted in Figure 6 are those that can have a negative effect on the patient's

ability to follow a medication regimen [321].

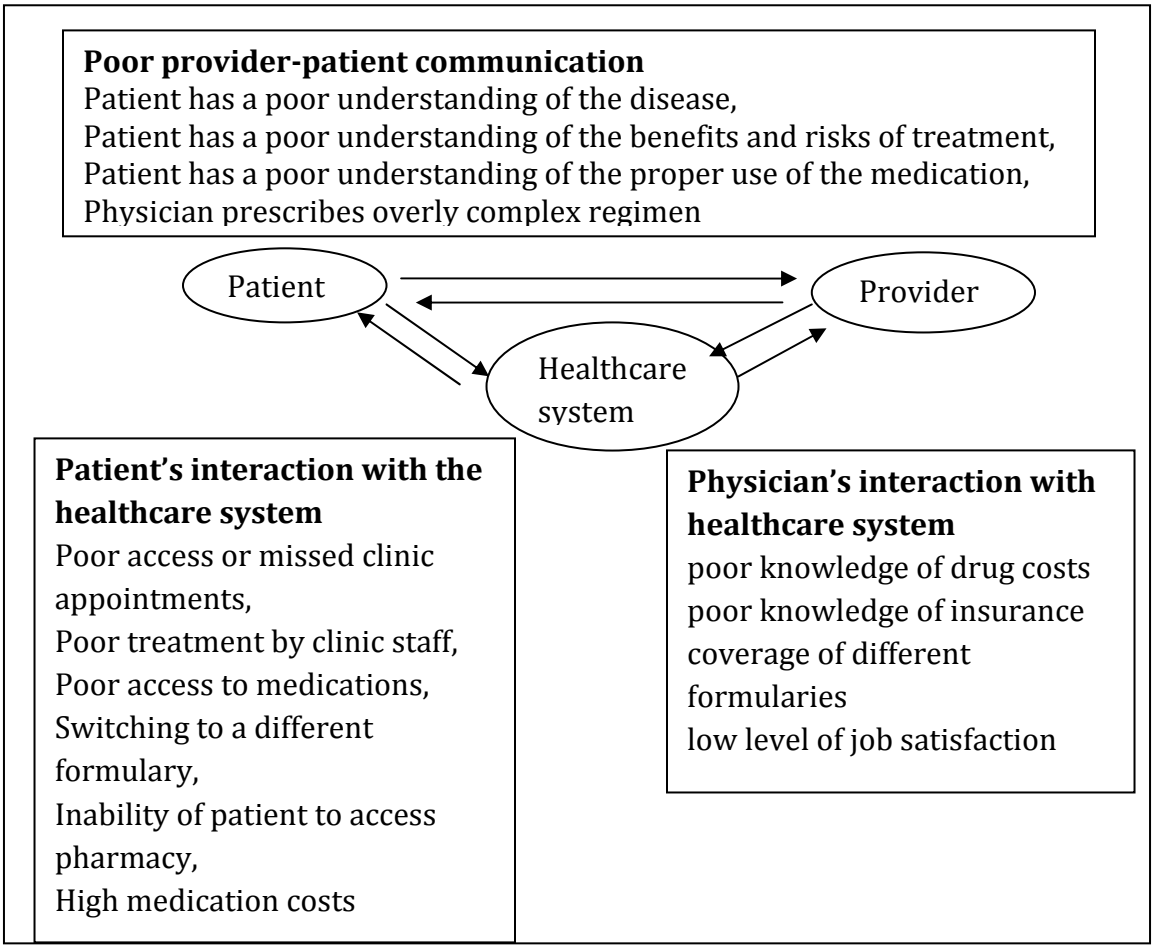


Figure 6 Barriers to Adherence: Interactions among Patient, Healthcare Providers, and Healthcare System
Source: [321]

2.2.5.4 Relationship Between Comorbidities and Medication Taking Behavior in Type 2 Diabetes

While depression has been documented to affect DM medication taking behavior [314, 315, 322], the presence and demands of other comorbid disease need to be investigated. Recently, there is an increasing attention on the relationship between comorbidities and medication adherence. However, an association between increasing comorbidity and DM medication adherence needs to be interpreted with caution because of inconsistent findings in the published literature.

Some studies reported that comorbidity places a significant detriment effect in DM medication compliance [54-58]. This is in part because as number of medical conditions increased, medication treatment becomes complex or intensive, which could result in a difficulty to compliance or because other medical conditions, such as depression and arthritis, impair patients' functioning and directly pose significant barriers to complete diabetes self-care tasks, such as medication taking [57-59]. Research showed that diabetes patients with a greater overall number of comorbidities placed lower priority on diabetes treatment and had worse diabetes self-management ability [59]. Also, with considering a fixed budget, diabetic patients with comorbid conditions may have to make difficult choices between forgoing necessary treatments for their diabetes, treatments for their comorbid conditions [184, 282, 323], which can result in poorer glycemic control, more symptoms, and poorer functioning [324, 325].

However, several studies found that increasing comorbidity burden were associated with higher medication adherence [60]. It is conceivable that patients with a higher number of chronic conditions could be better informed about diabetes and its complications and, therefore, would maintain greater rates of adherence despite their greater medication burden and numerous comorbidities. Also, increased perceived susceptibility and severity due to comorbid condition burden may motivate patients to improve their medication taking behavior.

Therefore, considering these inconsistent previous research findings, the impact of comorbidity on medication adherence among this population deserves to be explored further in detail.

2.2.5.5 Assessment of Medication Adherence among Diabetic Patients

Assessing patient medication adherence is important for both research and practice. In clinical practice, poor adherence leads to suboptimal treatment of medical conditions and may lead to adverse health outcomes and increased economic burden on the healthcare system [296, 326, 327]. The importance of measuring adherence is becoming increasingly recognized. The Health Plan

Employer Data and Information Set (HEDIS) quality measures use medication adherence as a metric to assess plan quality, which can impact payments made to health plans [328]. Also, Medicare is now paying providers for medication therapy management(MTM) services, and many MTM providers are developing specialized adherence interventions, which will increase the need for validated adherence measures for use by these practitioners, as well as those evaluating the impact of these new services [329, 330]. Moreover, in clinical research, poor adherence can reduce the statistical power to detect a difference between treatments and can affect study validity by increasing the risk of false negative results [331, 332].

However, lack of a "gold standard" in measuring medication adherence impose challenges and urges the need to devise a more appropriate, accurate, patient-friendly, convenient, and cost-effective measure [321]. The various medication adherence measures can be classified into direct and indirect techniques (table6) and each has own distinct combinations of advantages and disadvantages [321].

Direct methods include biologic assays of drug concentrations in blood and urine. Although this strategy provides an exact account of the drug and is not subject to patients' response bias, such measures are not used clinically for adherence monitoring because of the lack of available easy-to-conduct assays, prohibitive costs, or invasiveness of the procedure [321, 333, 334]. Also, such measures rely on the accuracy of the test and the extent to which a patient is adherent before test and may lead to an erroneous measurement [321].

Indirect measures can be classified into subjective measures (e.g., patient interviews, self-report and medication diaries) and objective measures (e.g., pill counts, pharmacy refill records, and electronic medication prescription monitors). Patient self-reported measures are less expensive but subject to social desirability and response bias [321, 333, 334]. Also, it has been found that agreement among such patient self-reported methods of measuring adherence was low and these measures tend to overestimate adherence [335]. Also, the accuracy of the results from such methods depends on patient's cognitive abilities and the honesty of their replies as well as interviewer's interpretation of patient responses [321, 333, 334].

Pill counts can be erroneous because patients often do not return the bottles that have the pill remaining or throw away the remaining pills in order to show adherence [321, 333, 334]. Electronic monitoring involves the use of a microprocessor that records the time and date when patient takes the dose[321]. Such microprocessors are lodged in the cap of the pill bottle without the cognizance of the patients [321]. A major assumption underlying this method is that patient takes the medication whenever the bottle is opened. Limitations of this method include cost of the monitors and impracticality of use [321].

Test	**Advantages**	**Disadvantages**
Direct Method		
Directly observed therapy	Most accurate	Patients can hide pills in the mouth and then discard them; impractical for routine use
Measurement of the level of medicines or metabolite in blood	Objective	Variations in metabolism and "white-cost adherence" can give a false impression of adherence; expensive
Measurement of the biologic maker in blood	Objective	Requires expensive quantitative assays and collection of bodily fluids
Indirect methods		
Patient questionnaires, patient self-reports	Simple; inexpensive; the most useful method in the clinical setting	Susceptible to error with increases in time between visits; results are easily distorted by the patient
Pill counts	Objective, quantifiable, and easy to perform	Data easily altered by the patient (e.g., pill dumping)
Rates of prescription refills	Objective; easy to obtain data	A prescription refill is not equivalent to ingestion of medication; requires a closed pharmacy system
Assessment of the patient's clinical response	Simple, generally easy to perform	Factors other than medication adherence can affect clinical response
Electronic medication monitors	Precise; results are easily quantified; tracks patterns of	Expensive; require return visits and downloading data from medication vials

	taking medication	
Measurement of physiologic markers (e.g., heart rate in patients taking beta-blockers)	Often easy to perform	Marker may be absent for other reasons (e.g., increased metabolism, poor absorption, lack of response)
Patient diaries	Help to correct for poor recall	Easily altered by the patient
When the patient is a child, questionnaire for caregiver or teacher	Simple; objective	Susceptible to distortion

Table 6 Methods of Measuring Adherence

Source:[321]

It has been emphasized that the choice of adherence assessment measure should be determined by considering several study features, including the overall goals of the study, the selection of the study population, the length of follow-up, and the assessment of exposed time to drug therapy, data availability and cost, and the relative advantages and limitations of the measures.

Selection of the study population for studies evaluating medication adherence entails the identification of patients dispensed the selected drugs during a specified study period. The length of follow-up and observation for studies evaluating medication adherence is also important to consider for three reasons. First, since small variations in the timing of refills may exist that may be unrelated to adherence (including titrations of drug dosage, patients going on vacations, short term hospitalizations); assessment of adherence over short time intervals is likely to be imprecise or unattainable through evaluation of pharmacy refill records. While definitive rules for all studies/drug classes are questionable, at a minimum, the time period for assessment/observation to determine medication possession rate-related measures or discontinuation/continuation rates should likely be equal to allow for a meaningful estimation.

Also, as in other epidemiologic studies, the observation time should be specified and consistent for all individuals, or methods should be used to account for differing lengths of follow-up (such as survival analysis techniques). The assessment of exposed time to drug therapy in studies employing automated databases is generally based upon the days supply of medication dispensed, the quantity of tablets dispensed, or a specified time period after each dispensing. The definition should be based upon the type if medication assessed, as well as the goals of the study and information available in the database. Measures of adherence are often based upon days supply information (medication possession rate, medication gaps, discontinuations), suggesting that the accuracy of the information on the days supply of medication should be considered.

In recent years, the use of administrative claim data as a source for calculating medication adherence has gained prominence. Administrative data sets, "data files generally compiled in billing for healthcare services," are often assessed in pharmacoeconomic and pharmacoepidemiologic research. Medication adherence measured using pharmacy claims has been validated using other adherence measures such as patient reports, pill counts, questionnaires, and interviews.

Obtaining medication adherence information from administrative data has some potential weaknesses and strengths. First, the adherence value based on administrative data does not provide medication consumption information, but rather provides assessment of possession. Second, medication intake calculations usually assume that patients consume the drug starting the day of dispensing, use the drug as prescribed, and consume all medications obtained. Administrative data can, therefore, provide the investigator only an estimate of the highest possible level of medication consumptions. A limitation of all adherence calculations of administrative data is the inability to determine whether the medication was ingested by the patient. In obtaining adherence values, administrative data analyses all assume that all medication is taken by the patient. The result is an overestimation of actual adherence and only provides a value of the medication obtained by the participant. Thus, reliance on administrative data may not enable the investigator to determine periods of under- or overuse of drug between refill

episodes. Moreover, in the cases in which the dosage prescribed (e.g., determining day's supply of medication obtained) is unavailable or unable to be determined, it is difficult to assess adherence using administrative data. Furthermore, the length of the assessment period may be problematic in the evaluation of adherence using administrative data, as both shorter (e.g., <60 days) and longer (e.g. >90 days) time periods introduce potential bias when estimating medication adherence. Also, adherence measures based on administrative data have not correlated with patient reported adherence. Lastly, administrative data have limitations in cases in which patients obtain refills from a variety of pharmacies, and they are not submitted as insurance claims or when patients pay out-of-pocket and no insurance claim is entered.

Despite these limitations, administrative data are convenient, noninvasive, objective, and inexpensive to obtain. Their ability to identify a large population of users of medications in a timely, efficient manner is highly advantageous. These databases are particularly suited for the evaluation of drugs intended for long-term therapy. Additionally, adherence estimates based on administrative data appear to be associated with clinical outcomes. Moreover, the estimates derived from the databases are more likely to reflect use in a real-world setting, compared to those obtained from populations participating in clinical trial settings. Furthermore, although estimates derived from studies using administrative data actually measure the acquisition of medication rather than consumption of medication, the derived measures can be considered to have a high specificity (identify those not consuming the medication) if the data are complete and patients are unlikely to obtain the medications from other sources not captured by the database. Therefore, administrative data are frequently used to obtain medication adherence information. Ideally, an adherence assessment from administrative data should provide an accurate reflection of the number of days the patient had correct dose of a drug available compared with the number of days the treatment was prescribed.

Despite these validation studies, there are no standards for the mathematical calculation of adherence using administrative data. A systematic review by Andrade et al. [336] identified 136 studies that employed administrative claims to calculate

medication adherence. About 57% of the studies considered medication possession ratio and related measures of medication availability (e.g., medication-total, proportion of days covered, adherence ratio), 10% used medication gaps, and 43% used switching and discontinuation in calculating medication adherence and persistence. Even among the 57% of the studies that considered medication possession ratio and related measures, the follow-up period definitions varied, ranging from a specified follow-up period definitions varied, ranging from a specified follow-up period of (e.g., 1 year), to period between first and last refill. The study emphasized the lack of consensus among methods used to calculate adherence. Another study published by Hess et al [337], identified 11 different adherence measures calculated using administrative claims data and subsequently initiated the idea of standardizing adherences measures. This study, however, did not empirically validate these measures to identify which of the measures may be preferred over others.

The most recent study published by Karve et al [338], identified 6 different adherence measures calculated using administrative claim data to assess the predictive validity of each adherence measure using hospitalization and nonpharmacy cost as the outcomes for adults with type 2 diabetes and on OAD medication treatment (table 7). Six adherence measures were the medication possession ratio (MPR), proportion of days covered (PDC), refill compliance rate (RCR), compliance ratio (CR), medication possession ratio, modified (MPRm), continuous measure of medication gaps (CMG), and continuous, single interval measure of medication acquisition (CSA). The results showed that multivariate models with MPR, PDC, CMG or continuous multiple interval measure of oversupply (CMOS) as adherence measures had the highest C-statistics of 0.701 in predicting diabetes specific hospitalizations. None of the adherence measures were significantly associated with nonpharmacy cost. Because MPR and PDC had the highest predictive validity for hospitalization episodes, this study suggested that these 2 measures should be considered first when selecting among adherence measures when using administrative prescription claim data.

Type of measure	Terminology	Description
Medication possession ratio and related measures of medication availability	Medication possession ratio, medication-total, proportion of days covered, adherence ratio, refill adherence, compliance rate, continuous multiple-refill-interval measure of medication availability, adherence index, compliance ratio, or compliance index	Generally defined as the proportion (or percentage) of days supply obtained during a specified time period or over a period of refill intervals. Two main definitions of Medication possession ratio (MPR): (1) MPR= number of days supply obtained during observation period number of days in observation period (2) MPR= number of days supply obtained (excluding last refill) number of days between first and last dispensing dates
Discontinuation/ continuation	Discontinuation, continuation, persistence	Generally defined by gaps between one dispensing of a drug and a subsequent dispensing, with continuous use based upon the days supply of medication dispensed, the quantity of tablets dispensed, or a specified time period after each dispensing; more liberal definitions are based upon a dispensing occurring during a specified time period
Switching	Switching	Few studies specified a time period after dispensing to evaluate a switch; often based upon a dispensing of a different drug at any time within study period
Measures based upon medication gaps	Medication-out, continuous measure of medication gaps (CMG), cumulative gap ratio	Generally determined for each refill interval using days supply information and the duration between refills; the proportion of days without medication during a specified time interval is then calculated
Refill adherence/ compliance or failure	Compliant fill rate, refill persistence, refill rate, renewal rate, refill failure, regularity of use	A number of different measures have been determined, including the proportion of total potential refills that are filled (or not filled) at an appropriate time interval (through a comparison of the day supply available to the number of days between fills) and refill rates or renewal rates during a specified time period
Retentiveness/ turbulence	Retentiveness, turbulence	Measures that describe the proportion of all subsequent dispensing within a specified time period that are duplicates (repeat pairs) or number of changes (additions, droppings, switches) occurring during a specified time interval

Table 7 Measures of Medication Adherence and Persistence Commonly Reported in Studies Using Automated Dataset
Source:[338]

Adherence measure	Formula
Medication possession ratio (MPR)	Number of days supply in index period/number of days in the study period (365 days)
Medication refill adherence (MRA)	[number of days supply in index period/number of days in the study period (365days)]×100
Continuous measure of medication acquisition (CMA)	Number of days supply/total days to next fill or end of observation period (365 days)
Proportion of days covered (PDC)	[Number of days supply in index period/ number of days in the study period (365 days)] ×100 capped at 1
Refill compliance rate (RCR)	(Number of days supply/last claim date - index date) × 100
Days between fills adherence rate (DBR)	1 – [(last claim date - index date) - total days supply/last claim date] index date] × 100
Compliance ratio (CR)	Number of days supply in the index period - last days supply/last claim date - index date
Medication possession ratio modified (MPRm)	[Number of days supply/(last claim date - index date + last days supply)] × 100
Continuous measure of medication gaps (CMG)	Total days of treatment gaps/total days to next fill or end of observation period (365 days)
Continuous multiple interval measure of oversupply (CMOS)	Total days of treatment gaps (+) or surplus (-)/ total days to next fill or end of observation period (365 days)
Continuous, single interval measure of medication acquisition (CSA)	Days supply obtained at the beginning of the interval/days in interval

Table 8 Mathematical Formulas for the Various Adherence Measures under Evaluation

Source:[338]

2.3. Theoretical Framework

This dissertation is a theoretically driven study to assess the effect of comorbidity in health-related behaviors and health-related outcomes. Two theories,

the modification of Health Belief Model by Becker and Maiman [63] and the Aday-Anderson's revised model for healthcare utilization, serve theoretical knowledge to construct our proposed model. The modification of the Health Belief Model by Becker and Maiman is used to explain sociobehavioral determinants of the health-related behaviors, while the Aday-Andersen's revised model is applied to explore potential determinants of the health-related outcomes. These two theories are combined to construct our proposed model for the understanding of potential pathways between comorbidity, health-related behaviors and outcomes. The following sections describe both the models in detail.

2.3.1. Health Belief Model

2.3.1.1 Health Belief Model

The Health Belief Model (HBM), a psychological model, is to explain an individual's health actions lying within the realm of "value-expectancy" models, which try to describe behavior or decision making under conditions of uncertainty [339-341]. Behavior is predicted from the value of an outcome to an individual, and from the individual's expectation that a given action will result in that outcome. The HBM was first developed to explain and predict who would utilize screening tests and/or vaccinations [342-344] and further extended to explain preventive action, illness behavior and sick-role behavior [342, 345, 346].

As assumed in the HBM, individuals will take actions to prevent illness if they feel that[347]: (1) they are at risk of developing a condition or contracting a disease, and that this risk is greater than their predisposed high risk attributed already to the condition or disease, (2) not taking the appropriate action would have serious consequences, (3) the proposed action will considerably reduce their susceptibility to or severity of the disease or condition, and (4) more benefit than harm in taking the proposed action.

The HBM identified six basic dimensions as a basis for behaviour [348]:

(1) Perceived threat: this consists of perceived susceptibility, which is patients' perception that they might contract a disease or condition

(2) Perceived severity: the patients; perception about significance of disease and consequences if untreated

(3) Perceived benefit: the patients' perception in regards to effectiveness of the action to reduce the threat of disease. The idea is that the patients will take an action in response to the perceived threat, and they will choose an action that they feel will be beneficial to them

(4) Perceived barriers: these include hindrance or barriers that stop the patient from taking the necessary steps to take action. It reflects the negative impact of recommended action if taken. The patients weigh the benefits and risks of the action to be taken

(5) Cues to action: patients' readiness to take any action is influenced by various factors, which serve as cues to initiate a particular action. These would be in the form of internal, such as physical sensation, or external, such as generated by mass media, stimulus to trigger the appropriate health behavior

(6) self-efficacy: this construct is defined as "the conviction that one can successfully execute the behavior required to produce the outcomes."

2.3.1.2 The modified Health Belief Model by Backer and Maiman for predicting and explaining compliance behavior

The modification of the HBM by Becker and Maiman attempted to assess social, psychological, and related factors which have been shown to consistently predict adherence and persistence [63]. The model is derived from extensive literature review which reflects that personal beliefs, faith in health related action, cost associated with action and social influences are significant predictors of adherence behavior. The Becker and Maiman model (Figure 7) is a three stage model comprising of 3 distinct steps. These main components of adherent behavior in the Becker and Maiman model are:

(1) **Readiness to undertake recommended adherent behavior**: the individual's subjective state of "readiness to take action" relative to a particular health condition, determined by both the person's perceived likelihood of

"susceptibility" to the particular illness, and by his or her perceptions of the probable "severity" of the consequences of contracting the disease. Theoretically, as display in Figure 7, this component is influenced by individual's psychological characteristics such as patients' motivations (concerns about health matters, willingness to accept and seek medical advice, intention to comply), value of illness treat reduction (patients' estimates of vulnerability, susceptibility, presence of symptoms, etc.) and patients' estimated probability that compliant behavior will reduce the threat of illness [63].

(2) **Modifying and enabling factors**: the individual's evaluation of the advocated health behavior in terms of its feasibility and efficaciousness (e.g., an estimate of the action's potential "benefits" in reducing susceptibility and/or severity), weighed against perceptions of physical, psychological, financial, and other costs or "barriers" involved in the proposed action. These are assumed to include demographics, structural, interaction, attitude, and enabling factors. The presence study will involve demographics, clinical and medication related variables as modifying and enabling factors in determining the patient readiness to undertake prescribed adherent behavior [63].

(3) **Compliant behavior**: this refers to the likelihood of the patients' adherence and persistence with preventive health recommendations and prescribed regimen. The modified model proposed in this study will examine patient outcomes, such as healthcare utilization and costs, as a result of adherent behavior [63].

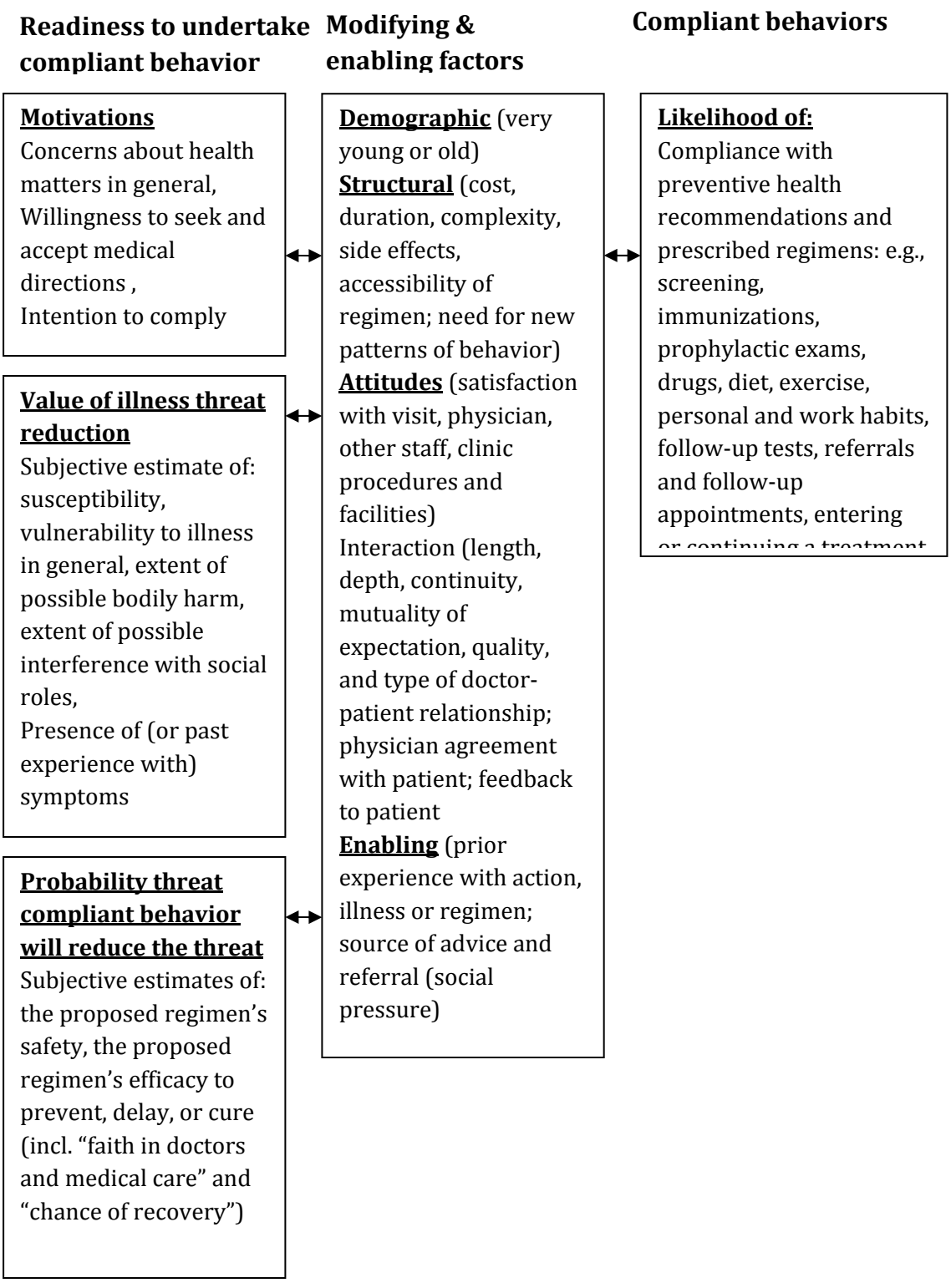


Figure 7 Modified Health Beliefs Model for Predicting and Explaining Compliance Behavior
Source: [63]

2.3.1.3 Application of the Health Belief Model to Type 2 Diabetes

It has been recognized that four constructs underlying HBM, including perceived susceptibility, perceived severity, perceived benefit, and perceived barriers, will help gain variation in explaining health-related behaviors among diabetic patients.

In the context of diabetes disease, perceived susceptibility with respect to diabetes can alter patients' risk of developing the disease. Perceived severity refers to the severity of diabetes and the complications associated with it. Perceived severity in diabetes patients would also include fear of diabetes-related hospitalization and/or fear of developing diabetes-related complications or comorbidities which may lead to hospitalization and additional healthcare costs. Perceived severity may motivate patients to improve their medication taking behavior. The perceived benefits associated with patients' action are improved glycemic control, reduced healthcare costs, reduced hospitalizations and emergency room visits, and better quality of life. Patients may face different barriers like unwanted side-effects, difficult dosing regimen, lifestyle and dietary modifications, and costs of medications. Disease management programs, pharmacist counseling, and diabetes education will provide cues to action. One the basis of an extensive literature review, Gentili et al stated that the HBM can be applied to diabetic patients to study medication use behavior and relevant issues [69].

2.3.2. The Aday-Anderson's Revised Model for the Healthcare Utilization

The Aday-Anderson's revised model for explaining healthcare utilization (Figure 8) has been widely used to predict or explain the medication use behavior as well as the healthcare service utilization behavior. This model demonstrates healthcare-seeking behavior by classifying determinants of healthcare utilization into predisposing, enabling, and need-related factors. The model can serve a conceptual framework to assess the impact of these determinants (predisposing, enabling, and need factors) on health-related behaviors and subsequently on health-

related outcomes [64]. The following description explains these three aspects of determinants in detail.

(1) **Predisposing factors** indicate the propensity of a person or group to utilize healthcare services. Propensity toward use can be predicted by individual characteristics which exist prior to the onset of illness. These factors include demographics, social structure and attitude-belief variables. Some examples of predisposing characteristics are patient's age, gender, and race/ethnicity [64].

(2) **Enabling factors** refer to the variables that affect patient's ability to gain access to healthcare services, including income, healthcare insurance status, access to care and source of care [64].

(3) **Need factors** can be defined as an individual's health status as he or she perceives it and/or as evaluated by a healthcare provider. Some of the need characteristics could be perceived health status, medical condition, severity of illness, the presence of comorbidities, and quality of life [64].

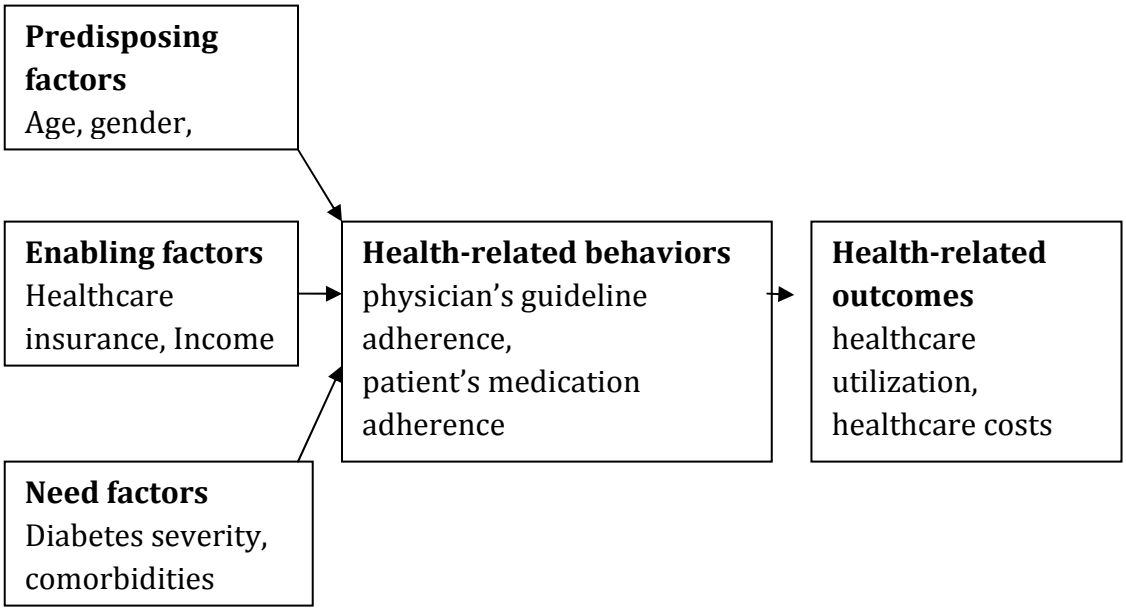


Figure 8 Aday-Anderson's Revised Model for Determinants of Healthcare Utilization
Source:[64]

2.3.3. Proposition of Theoretical Model

Our conceptual framework was based on two theories- the modification of the HBM by Becker and Maiman [63] and Aday-Anderson's model for healthcare utilization [64]. The present study was aimed to assess the impact of comorbidity on health-related behaviors and outcomes, adjusting for other potential influential factors.

Underlying assumption by the HBM [347] is that patients' willingness to undertake adherent behavior where willingness is based on their perceptions of severity, susceptibility, benefits, and barriers. The modifying and enabling factors were derived from modified model by Becker and Maiman [63]. The modifying and enabling factors considered in this study were demographic factors (age, race, sex), clinical variables (diabetes disease severity and comorbidity), medication-related such as the number of prescription medications, the number of therapeutic class of medications and system related variables such as healthcare insurance coverage, type of healthcare plan, and source of care. Health-related behaviors were considered two aspects of factors-physicians' adherence to diabetes treatment guideline and patient's adherence to diabetic medications. Particularly, medication adherence behavior was measured using the Medication Possession Ratio (MPR) by evaluating medication refill patterns. The economic outcomes measured were healthcare service utilization, including the likelihood of ER visit, the hospitalization and the number of outpatient visits, and healthcare cost, including total healthcare and diabetes-related costs.

Also based on the Anderson's model [64], the impact of the determinants, in terms of predisposing, enabling, and need aspects of factors, on the health-related behaviors, including physician's and patient's adherence behaviors, and subsequently the influence of health-related behaviors on healthcare related outcomes were examined. Also, the pathways from those determinants to the healthcare outcomes was assessed to determine whether the effects of these factors on the healthcare outcomes are completely or only partially mediated by health-related behaviors, or even completely independent of health-related behaviors. The following figure captures the theoretical framework for this study.

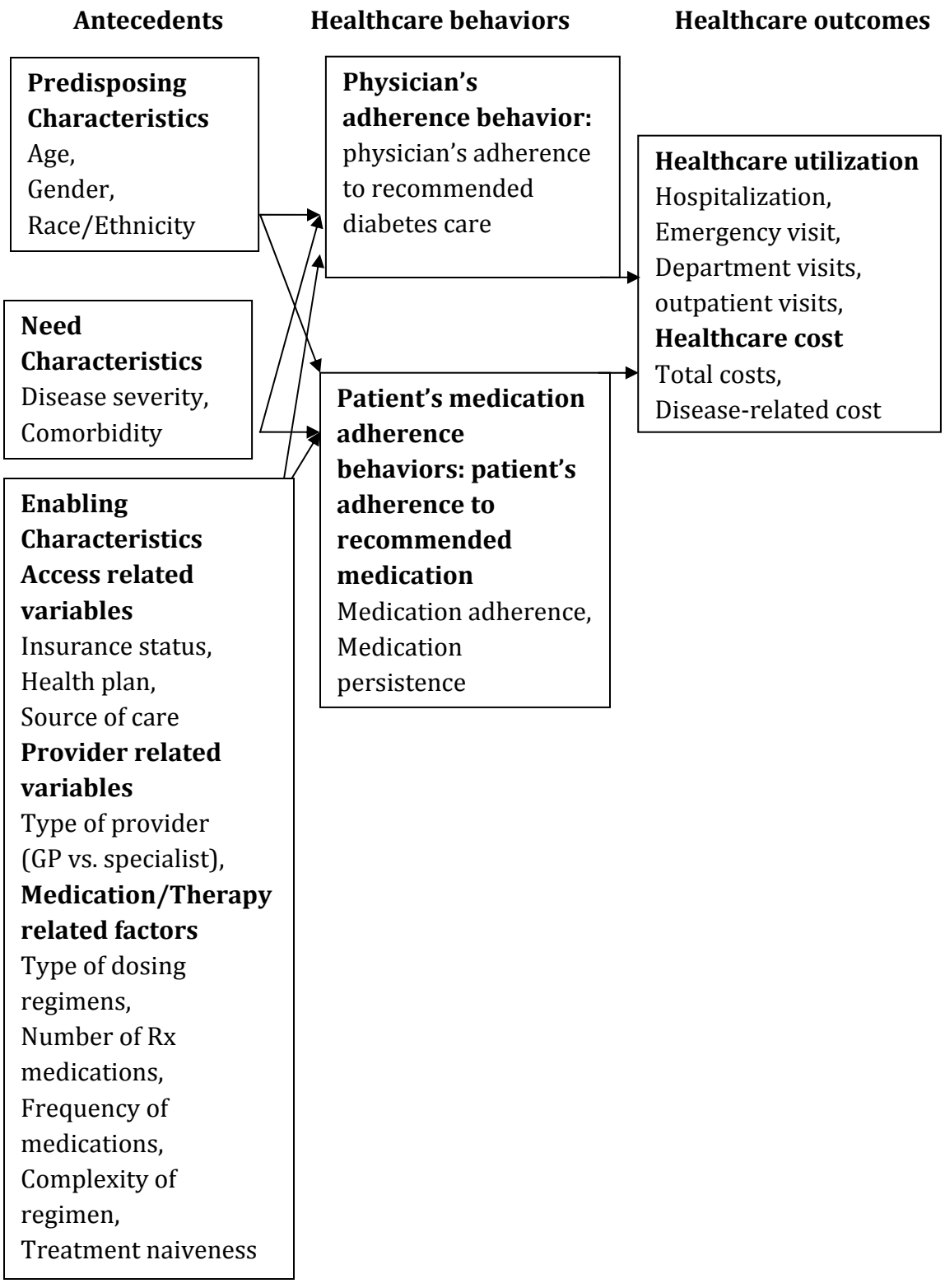


Figure 9 Conceptual Framework Under This Study

Chapter
3. Methods

This chapter provides detailed information about the data source, study design, study population, hypothesis testing and statistical analysis performed in the present study.

3.1. Database and Management

3.1.1. Data Source

The Medicaid program is a jointly funded cooperative venture between the Federal and State government to assist States in providing medical and health services to vulnerable population. It primarily covers 5 broad groups including children, pregnant women, adults with dependent children, individuals with disabilities, and elderly individuals below certain poverty level [349].

Medicaid serves 50 million Americans, with a growing percentage enrolled in managed care [349]. The HEDIS clinical and access to care results for Medicaid managed care plans are more variable and, with few exceptions, less favorable than for Medicare and commercial plans [350]. Patient data are available and have been used to study factors contributing to differences in adherence to recommended quality standards among Medicare beneficiaries [351-353]. Individual-level analyses for Medicaid populations are less common. Medicaid plans cover lower income, more ethnically diverse populations and have higher percentages of participants with chronic illness, multiple chronic conditions, disabilities, severe mental illness, and substance use disorders than commercial plans [42]. All of these factors can influence adherence to quality standards, making it difficult to generalize findings from studies of Medicare and commercial plans to those serving Medicaid populations [43-47]. Co-occurring physical and behavioral disorders, which

increase the complexity of treatment and raise the risk of adverse events, represent a particular challenge for providers [47]. Therefore, Medicaid population is unique in terms of comorbidity research as the beneficiaries comprise of vulnerable population affected multiple medical conditions.

The database used for this study was the MarketScan™ Medicaid database licensed from Thomson MedStat. This database contains the medical, surgical, and prescription drug experience of nearly 22 million Medicaid enrollees from 8 different states of varying size and dispersed all across the US. Although the states are de-identified, the data consist of at least one state from each US region. The MarketScan™ Medicaid database includes records of inpatient services, inpatient admissions, outpatient services, ad prescription drug claims, as well as information on long-term care and other medical care. Data on eligibility (by month) and service and provider type are also included. In addition to standard demographic variables such as age and gender, the database includes variables of particular value to researchers investigating Medicaid populations, such as aid category (blind/disabled, Medicare eligible) and race [354]. For the purpose of this study, the Medicaid database was updated and queried from January 1, 2003 to December 31, 2007.

The MarketScan™ databases are the Health Insurance Portability and Accountability Act (HIPAA) compliant and features encrypted member and service provider identification numbers. There are several distinct advantages of MarketScan™ claims data over other types of data sources. (1) Large sample size. This database offers the largest convenience sample available in proprietary databases with 69 million unique patients since 1996. In the most recent data year, this database contains data on 29 million covered lives. It sample size is large enough to allow creation of a nationally representative data sample of American with employer-provided health insurance and Medicaid; (2) Complete episodes of care. MarketScan™ claims data capture the full continuum of care in all settings, including physician office visits, hospital stays, retail, mail order, specialty pharmacies, and carve-out care. Linking hospital discharge records with claims data at the patient level has significantly increased the capability of MarketScan™ data to

capture the continuity a patient's drug therapy between the inpatient and outpatient setting; (3) Longitudinal tracking at the patient level. The stability of MarketScan™ data source allows superior continuity of patients over multiple years, generally longer than other claims data because majority of MarketScan™ data sourced from large employers. Employer-provided data also allow tracking of patients across health plans. This tracking ability is useful because people change health plans more often than they change jobs, and these data are able to capture patients who are lost in plan-based data sources-17% of patients in those data. In the most recent five years of MarketScan™ Commercial and Medicare Supplemental data, nearly 29 million patients (73%) have at least 12 months of continuous enrollment; (4) Detailed prescription drug information. The MarketScan™ claims data contain complete information on outpatient prescriptions. MarketScan™ data allow identification of type of disease (from medical claims) and can be used to determine whether clinical, demographic, and provider characteristics influence prescribing patterns. Because individual patients' prescription fills are recorded, therapies prescribed concurrently (and presumably used in combination) can also be identified. This provides valuable information about actual drug use patterns, as opposed to other databases that track only prescription fills. (5) The MarketScan™ Hospital Drug Database provides researchers with inpatient drug utilization data derived from hospital discharge records. These data and a proprietary projection methodology allow researchers to understand drug use in the inpatient and outpatient environment including hospital use patterns, switching behavior, combination therapy, and patient characteristics to help determine if introduction or earlier use of a product would improve clinical and overall cost outcomes and to analyze diagnosis volumes. (6) High-quality coding. A major advantage of MarketScan™ claims data involves their comprehensive and high quality coding. Key examples include: diagnosis coded on 99% of all claims; procedure coded on 85% of physician claims; fully paid and adjudicated claims; complete payment/charge information, including amount of patient responsibility; complete outpatient prescription drug information, including patient copayments, mail order,

injectables, specialty pharmacies, all carve-outs, manual and electronically submitted claims, and plan/formulary summaries [355].

As with any data source, MarketScan™ claims have limitations. Some of these have to do with the nature of claims data, and other with the nature of MarketScan™ sample population. Two limitations are as follows: (1) the MarketScan™ claims are based on a large convenience sample. Because the sample is not random, it may contain biases or fail to generalize well to other populations.(2) the data come mostly from large employers; medium and small firms are not represented [355].

Numerous research applications have been based on the MarketScan™ claims databases because its features enable analysts to conduct a broad range of health services studies, including cost-effectiveness and cost-offset studies, pharmacoenomic outcomes evaluations, burden of illness analyses, surgical and pharmaceutical treatment comparisons, forecasting and modeling, assessment of best practices and benchmarking against empirical norms or clinical practice guideline, and clinical trial planning and support [355].

3.1.2. Construction of MedStat MarketScan™ Medicaid Database

The MarketScan™ Database are constructed by collecting data from employers, health plans, and state Medicaid agencies and comprise service-level claims for inpatient and outpatient services and outpatient prescription drugs. Financial, clinical, and demographic data are standardized to common definition. Drug detail (e.g. therapeutic class, therapeutic group, manufacture's average wholesale price, and a generic product identifier) and clinical detail (on disease episode grouper) are also added.

A unique enrollee identifier, a personal level identifier, is assigned to each individual in a MarketScan™ claim database. This identifier is created by encrypting information provided by data contributors. This information includes the employee identifier, the relationship of the enrollee to the contract holder, the gender of the enrollee, and the enrollee's date of birth. The standardized fields of the individual databases are combined and links between years of data and across all data types

are also created. So, individuals can be tracked longitudinally over the years and across all the tables including pharmacy, medical/surgical data, but can not be linked to receipt ID, social security number, or any other external identifier. To protect the privacy of patient data, the MarketScan™ research databases fully comply with the HIPAA of 1996. The MarketScan™ data is the HIPAA compliant and features encrypted member and service provider identification numbers; all patient-level and provider-level data within the MarketScan™ research databases contain synthetic identifiers to protect the privacy of individuals and data contributors.

The end product of the MarketScan™ claims data is one of the nation's largest collections of patient data, featuring: an opportunity sample from multiple sources (employers, states, health plans), over four billion patient records, 69 million covered lives, 77 contributing employer; 12 contributing health plans, and representation from over 126 unique carriers. The MarketScan™ warehouse consists of 8 claims databases, including Commercial Claims and Encounters[10], Medicare Supplemental and Coordination of benefits (COB)[11], Health and Productivity Management (HPM)[12], Benefit Plan Design[13], Health Plan, and Medicaid. (see Figure 10). Only Medicaid database is used by present study.

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[10]This database consists of employer- and health plan sourced data containing medical and drug data for several million individuals annually. Nearly 18 million individuals are included in the 2006 database, encompassing employees, their spouses, and dependents who are covered by employer-sponsored private health insurance. Healthcare for these individuals is provided under a variety of fee-for-service (FFS), fully capitated, and partially capitated health plans, such as preferred and exclusive provider organizations (PPOs and EPOs), point of service plans. Medical claims are linked to outpatient prescription drug claims and person-level enrollment information.

[11] This database is the first in the United States to profile the healthcare experience of retirees with Medicare supplemental insurance paid for by employers. The database includes the Medicare-covered portion of payment (represented as Coordination of Benefits Amount, or COB), the employer-paid portion, and any patient out-of-pocket expenses. The Medicare Supplemental database provides detailed cost, use, and outcome data for healthcare services performed in both inpatient and outpatient settings. For most of the population, the medical claims are linked to outpatient prescription drug claims and person-level enrollment data through the use of unique patient or enrollee identifiers. Beneficiaries in the MarketScan Medicare Supplemental database have drug coverage; therefore, drug data are available and provide additional valuable information. This feature makes the database a powerful tool for pharmacoeconomic and outcomes research and provides valuable insight into the drug use and spending patterns of older Americans.

[12] This database provides the opportunity to combine data on workplace absence, short-term disability, and workers' compensation with medical/ surgical claims and outpatient drug data. The

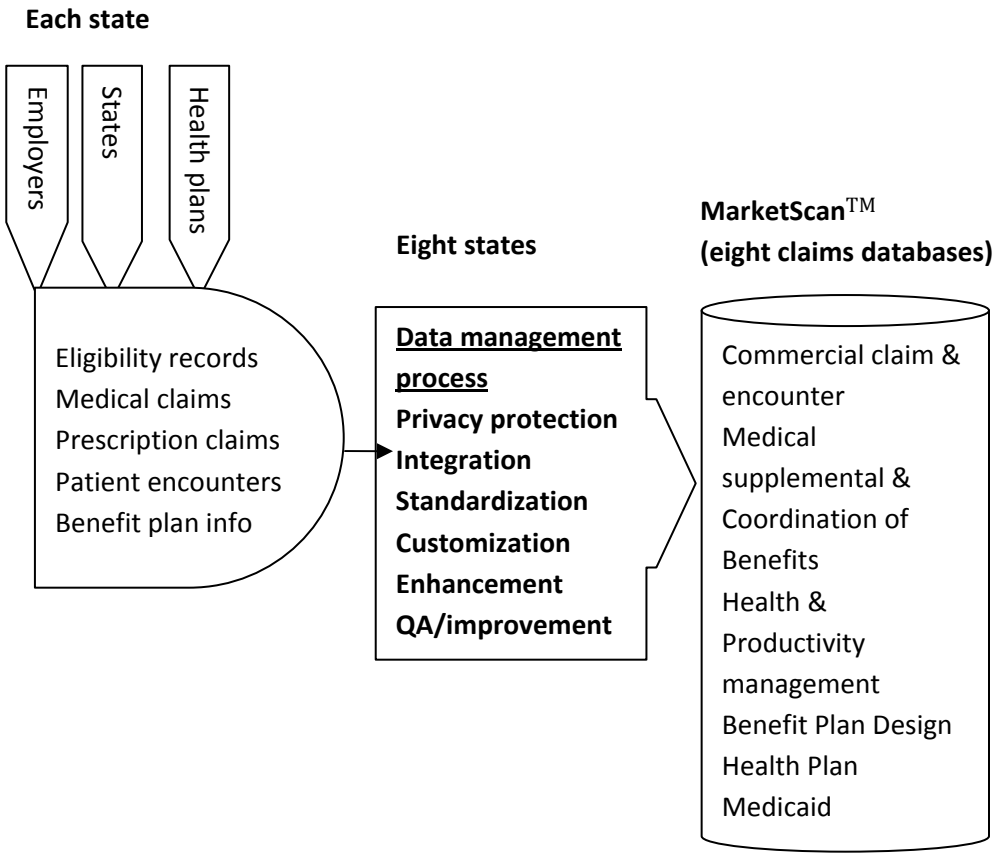

Figure 10 MarketScan™ Claims Databases: Fully Integrated at the Patient Level

3.2. Study Design

3.2.1. Study Population

The study population comprised of Medicaid eligible patients aged 18 to 64 years old diagnosed with type 2 diabetes and starting a new oral antidiabetic medication (SUs, MET, and TZDs) during July 1, 2003 to December 31, 2006. The

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database allows researchers to assess both the direct and indirect costs associated with a particular condition or treatment

[13] This database contains detailed information about benefit plan characteristics for a subset of the health plans represented in the Commercial and Medicare Supplemental databases. The Benefit Plan Design database allows researchers to:

- Evaluate the impact of health plan features on healthcare utilization
- Assess the relative performance of plan types with varying managed care features
- Include detailed plan provisions – such as copayments, deductibles, and coverage options –in analysis of healthcare cost and use
- Measure changes in plan design and benefit characteristics from 1995 onward

study protocol was exempted by the Institutional Review Board (IRB) at the University of Michigan. In the following, the terminologies used for inclusion/exclusion criteria were explained first and study criteria were then specified.

Definitions of terms used in study criteria:

Monotherapy: an OAD medication with a single drug regimen

Study period: from January 1, 2003 to December 31, 2007. Entire study period was further classified into three specific periods:

(1) Identification period: the period from January 1, 2004 to December 31, 2006 was used to identify new start of the OAD medication.

a. **Index date:** date of the first OAD prescription claim during the identification period for patients who remain on the same medication therapy throughout the study period

b. **Index prescription**: the first OAD medication for patients identified during identification period and remaining on the same medication therapy throughout the study period

(2) Pre-index period: 12 months prior to the index date. This was used to verify continuous Medicaid eligibility of patients as well as control for baseline characteristics before starting any therapy, such as predisposing, need and enabling variables as specified in our theoretical model. Also, this helped determine patients who did not have any OAD claims in this period and confirm a new start of the OAD medications in the index date.

(3) Post-index period: this period begins after the patient's index date and extends until the end of the study duration. It was used to ensure that the patients had at least 12 months of follow-up period, such as continuous medication prescription. Health-related behaviors (e.g., medication taking behavior) and outcomes (e.g., costs) were examined in this period.

Drug naïve patients: patients with no OAD prescriptions in the pre-index period.

Continuous Medication therapy: was defined by the following criteria:

(1) Therapy without a lapse of> 60 days between date of days' supply expiration of any prescription fill and the subsequent claim date (days between end date of first fill and date of next fill), **and**

(2) At least 2 prescription on the index medication

3.2.2. Inclusion Criteria

The following inclusion criteria were used for the selection of study subjects:

1. **Patients with continuous Medicaid eligibility in the pre- and post-index periods (12 months before and after the index date).** The continuous enrollment criteria ensure that all patients had the same follow-up period and reduce bias due to failure to follow-up.
2. **Patients with type 2 diabetes diagnosis.** Patients were identified using the *International Classification for Disease Code-9th revision Clinical Modification* (ICD-9-CM) for at least one primary or secondary diagnosis of type 2 diabetes (250.0x-250.9x, where x=0 or 2) from outpatient or inpatient claims during January 1, 2003 and December 31, 2007.
3. **Patients aged 18 to 64 years old at the index date.** The reason for excluding patients aged 65 years and above was that these patients may be dual beneficiaries (Medicare and Medicaid enrollees) and therefore obtaining complete data on these patients may not be available.
4. **Drug naïve patients in the pre-index period.** This criteria concerns that newly treated patients beginning their first course of medication (first-line patients) are likely to have significantly different medication use behaviors and responses to medication than are those who are on a particular therapy already. The current study included only newly started cases to understand the medication use behavior of patient who are naïve to the OAD.
5. **Patients starting OAD medication therapy during the index period window** (January 1, 2004 to December 31, 2006)

6. **Patients were only prescribed the monotherapy of OAD medications**, including SU, TZDs, and MEF, **during the index period.**
7. **Patients with continuous medication therapy**

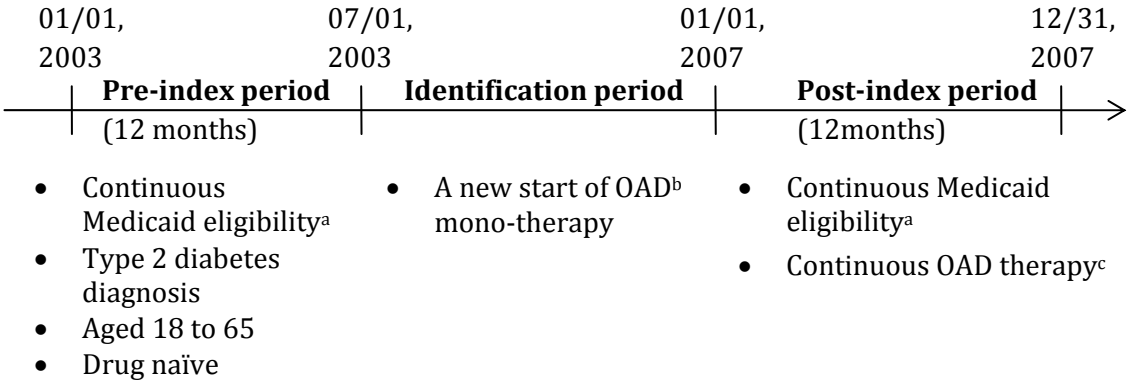
3.2.3. Exclusion Criteria

The following criteria were used to filter out the final cohort

1. **Patients with dual eligibility** (Medicaid and Medicare coverage). These patients also get reimbursed by Medicare hence it is difficult to get complete healthcare utilization data for them. These dual eligible patients mainly include elderly aged 65 years and above, and disable individuals. Hence, the subjects of this research were limited to only Medicaid recipients younger than 65 years. Also, patients 18 years and younger were excluded because the present study was intended to focus on adult and because those patients were more likely to be type 1 diabetes.
2. **Patients diagnosed with type 1 diabetes** (ICD-9-CM=250.0x-250.9x, where x=1 or 3) or **gestational diabetes** (ICD-9-CM=648.8x, where x=0-9). These patients were excluded from the study as they were mainly using insulin therapy and the primary objective of this study was to measure OAD medication adherence.
3. **Patients who were already on OAD medication therapy (established patients) in pre-index period**.
4. **Patients were prescribed insulin therapy**. The reason for excluding these patients is that these are high risk patients whose level of severity is high compared to those on oral therapy. Additionally, medication use behavior for patients on insulin therapy is substantially different from those on oral medication due to complexity of dosing regimen. Moreover, the dataset does not provide sufficient information for calculating medication adherence for insulin therapy so it is difficult to measure medication adherence of patients on insulin therapy

5. **Patients on the OAD medications that were other than SUs, MET, and TZDs**. Research have shown that there are very few patients on meglitinides and α-glucosidase inhibitors; these patients were not included in the study cohort

   The patient selection criteria in relation to study period were described in Figure 11 and the steps of the selection of final cohort were showed in Figure 12.



a: Medicaid ad Medicare dual eligible patients were excluded from study
b: Only target three OADs: SUs, MET, and TZDs
c: Continuous OAD therapy: therapy without a lapse of> 60 days between date of days' supply expiration of any prescription fill and the subsequent claim date (days between end date of first fill and date of next fill), and at least 2 prescription on the index medication

Figure 11 Study Subject Eligibility Criteria Corresponding to Study Period

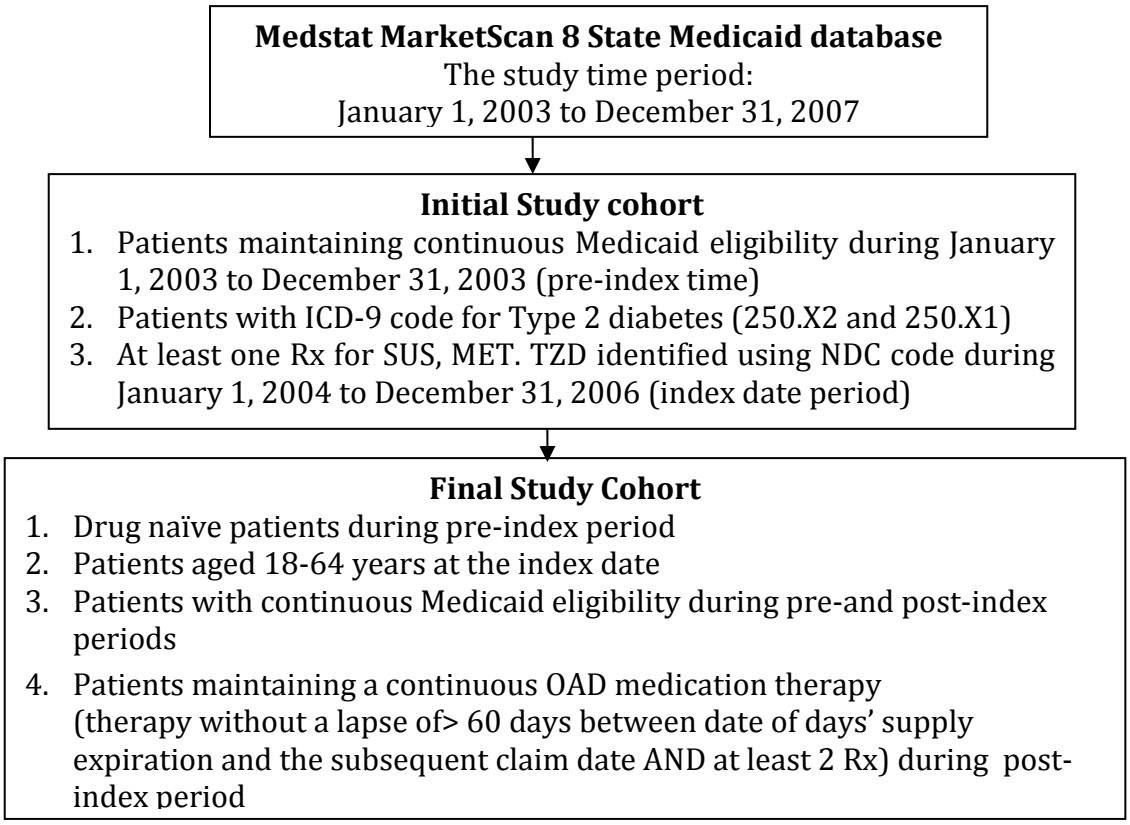


Figure 12 Identification of Study Cohort

3.3. Study Perspective

The study was conducted from the payer's perspective, the payer being Medicaid programs. Medicaid programs offer national health assistance for individuals and families with low incomes (elderly, blind, or disabled) and for members of families with dependent children. Programs are funded by the federal government and the states. Reimbursements are made on a retrospective, fee-for-service basis, with payments limited to the lower end of the usual charge of the pharmacy that fills the prescription or to the pre-established Medicaid rate ($1-$4). Some programs also pay for hospitalizations, emergency room visits, and physician visits for eligible patients

The reason for choosing payer's perspective is that the benefits associated with improved health-related behaviors, such as healthcare providers' adherence to

practice guideline and patient's medication adherence, may potentially reduce healthcare costs and resource utilization. Lower costs and resource use would mean lower reimbursements by Medicaid. It will be beneficial in making informed decisions about coverage to members as well as develop interventions to improve medication use in type 2 diabetic patients.

3.4. Data Elements

The study variables were retrieved from the multi-state Medicaid database, which mainly consists of following files, including inpatient services, outpatient drug claims, annual summary enrollment and detail enrollment files. Variables obtained from database were demographics (e.g., age, gender, race/ethnicity), clinical characteristics (e.g., primary and secondary diagnosis, comorbidities, type of pharmacotherapy), and healthcare utilization (e.g., emergency room visit, hospitalization, healthcare cost). Selected information was outlined in table 9.

File	Record description	Coding	Format
Enrollment detail			
	Enrollee ID	ENROLID	----
	Eligibility start date	DTSTART	mmddyy10.
	Eligibility end date	DTEND	mmddyy10.
	Birth year	DOBYR	CCYY
	Gender	SEX	1: Male 2: Female
	Race/ethnicity	STDRACE	1: White 2: Black 4: Hispanic 9: Other
	Medicaid eligibility category	BOE	1: Aged Individual 2: Blind/Disabled Individual 4: Child (not Child of Unemployed Adult, not Foster Care Child) 5: Adult (not based on unemployed status) 6: Child of Unemployed Adult (optional) 7: Unemployed Adult (optional) 8: Foster Care Child 9: Eligibility status Unknown (counts against error tolerance) A: Individual covered under the Breast and Cervical

			Cancer Prevention and Treatment Act of 2000
	Medicare eligibility	MEDICARE	0: Not dual eligible for Medicare 1: Dual eligible for Medicare
	Medicaid capitation flag	CAP	0: Fee-for-service 1: Capitated
Outpatient services			
	Enrollee ID	ENROLID	----
	Date of service incurred	SVCDATE	mmddyy10.
	Date of service ending	TSVCDAT	mmddyy10.
	Primary diagnosis	DX 1	
	Secondary diagnosis	DX 2	
	Procedure code type (CPT)	PROCTYP	*: ICD-9-CM 1: CPT 3: UB92 Revenue Code 6: NABSP 7: HCPC 8: CDT (ADA)
	Procedure 1	PROC1	Procedure code
	Cost/reimbursed amount (pay)*	PAY	Each character = 0-9. Represented in dollars and cents with an explicit decimal point.
Inpatient services			
	Enrollee ID	ENROLID	----
	Admission date	ADMDATE	mmddyy10.
	Discharge date	DISDATE	mmddyy10.
	Principal diagnosis	PPROC	**
	Procedure 1	PROC1	Procedure code
	Diagnosis 1 and diagnosis 2	DX1 And DX2	
	Procedure code type (CPT)	PROCTYP	*: ICD-9-CM 1: CPT 3: UB92 Revenue Code 6: NABSP 7: HCPC 8: CDT (ADA)
	Cost/reimbursed amount (pay)*	PAY	
	Place of service	STDPLAC	Codes 01- 19 indicate that place of service was inpatient, and codes in the range of 20 and above indicate outpatient.
	Type of service	STDSVC	
	Type of provider	STDPROV	001-099 Facility 100-799 Physician

			100-199 Non-admitting Physicians 200-499 Admitting Physicians 500-599 Surgeons 800-899 Professionals (Non-Physician) 900-999 Agencies
	Diagnosis related group	DRG	
	Length of stay (days)	DAYS	Each character = 0-9
	Quantity of service	QTY	Each character = 0-9
	Discharge status	DSTATUS	01: Discharged to home self-care 02: Transfer to short-term hospital 03: Transfer to SNF 04: Transfer to ICF 05: Transfer to other facility 06: Discharged home under care 07: Left against medical advice 08-19: Other alive status 20-29: Died 30-39: Not Yet discharged/Transferred 40-42: Other died status 50: Discharged to home (from Hospice) 51: Transfer to medical facility (from Hospice) 61: Transferred to Medicare approved swing-bed 71: Transfer/referred to other facility for output svcs 72: Transfer/referred to this facility for output svcs 99: Transfer, identified through Hospital ID MDST change Missing: Invalid
Outpatient pharmacy claims			
	Enrollee ID	ENROLID	----
	Date of service incurred	SVCDATE	mmddyy10.
	National Drug Code	NDCNUM	Each character = 0-9
	Days supply	DAYSUPP	Each character = 0-9
	Costs (pay)*	PAY	
	Generic indicator	GENIND	1: Single source brand 2: No longer used 3: Brand name, generic available 4: Multi source generic 5: Single source generic 6: Over the counter

			7: Other/unavailable Missing: not tagged
	Generic product ID (OTC medications)	GENERID	Each character = 0-9
	Dispensing fee	DISPFEE	Each character = 0-9.
	Quantity of service	QTY	Each character = 0-9

* Gross payments to a provider for a service. Payment equals the amount eligible for payment under the medical plan terms after applying rules such as discounts, but before applying COB, Copayments, and Deductibles.

** Usually a CPT4 code. ICD-9-CM codes and HCPC codes appear occasionally. PPROC = PROC1 only on the Inpatient Admissions (I) Table.

Table 9 Selected Records Retrieved from the Medicaid Database

3.5. Analytical Framework

Target population: adults who were aged 18 to 65 years old with type 2 diabetes prescribed oral OAD medication in a Medicaid setting

Outcomes:

Healthcare related behaviors:

(1) Physicians' adherence with diabetes treatment guideline: physician's treatment compliance score was calculated as the number of the American Diabetes Association (2005) recommended examinations [204], including (1) at least two hemoglobin tests, (2) a cholesterol test, (3) an eye examination, (4) a mircoalbuminuria test and (5) a foot examination. The final compliance scores were then calculated by adding up the number of treatment guidelines completed. Excluding HbA1c, a person receiving the same treatment multiple times in the allotted time was only given credit for it once. For example, a person who had two cholesterol screening was only given credit once. Treatment compliance scores could range from zero (no treatments) to five (all recommended numbers of treatments were received).

(2) Patient's medication adherence specific to SUs, MET, and TZDs

Healthcare related outcomes

(1) Healthcare utilization, including the numbers of hospitalization, emergency room and outpatient visits during post index period

(2) Healthcare costs, including total healthcare cost and diabetes care related cost, during post index period

Covariates:

Predisposing variables: patient's age, gender, race/ethnicity

Need variables: diabetes disease severity, comorbidity

Enabling variables:

(1) Access-related variables: healthcare insurance status, health plan, source of care

(2) Provider-related variables: type of provider (GP vs. endocrinologist)

(3) Medication/therapy related variables: type of dosing regimens, number of Rx medications, frequency of medications, and complexity of regimen.

The steps involved in the creation of analytic al dataset and resulted sample estimation were described below in Figure 13.

Step 1: There were 714,648 receipts with type 2 diabetes diagnosis from January 1, 2003 to December 31, 2007. Among these patients, 240,594 receipts with type 1 diabetes or gestational diabetes diagnosis were excluded, resulting into 581,930 receipts.
Step 2: 534,210 receipts were set with outpatient pharmaceutical claims database to identify claims for OAD medications. Only drug claims that had NDC codes for SUs, MET, and TZDs during January 1, 2003 to December 31, 2007 were included, which produced 278,246 receipts. Among them, 31,161 receipts who only used one of index drugs once during entire study period were therefore excluded.
Step 3: we further included 91,648 patients who newly started OAD medication during January 1, 2004 to December 31, 2006 (index identification period) by excluding patients who had any pharmacy claims during 12 months before the index date.
Step 4: we excluded 24,767 receipts using insulin therapy, which resulted into 66,881 receipts who took at least one of index prescriptions. Among them, 53,966 patients only used one of three index prescriptions (1,716 Met users, 40,040 Sulf users, and 12,210 TZD users), 12,915 patients only two index prescriptions (2,843 patients who used Met plus Sulf, 1,089 patients who used Met plus TZD, and 8,983 patients who used Sulf plus TZD), and 1,949 patients have used three index prescriptions during January 1, 2004 to December 31, 2006.
Step 5: only 25,657 receipts with continuous Medicaid eligible for 12 months before and 12 months after the index date were retained in the dataset with the help of monthly eligibility indicator.
Step 6: There were 14,317 patients who were dual eligible (both Medicaid and Medicare) and therefore excluded from the study, resulting into 11,340 receipts.
Step 7: we excluded receipts aged less than 18 (#=1,180) or orlder than 64 (#=218) years old and those who had more than one birthday records (#=10) during entire study period, which resulted in a final sample of 9,832 with age between 18 and 64 at index date.

Figure 13 Study Steps Involved in Creation of the Analytical Dataset

3.6. Measurement of Study Variables

The study variables created from the dataset were described in the table 10.

Variables	Coding	Description	Working definition
	Enrolid	Medicaid ID	-------
	Index_yr	Index year	-------
Predisposing	**Ageatsta**	Age at the start of the first OAD therapy	the year of index date*– the year of birth
	D_gend	Gender identified at the start of the first OAD therapy	If gender=male then d_gend=0; if gender=female then d_gend=1
	D_stdrace	Race/Ethnicity of the patient identified at the start of therapy	If Race=White then d_stdrace=0; if Race=Black then d_stdrace =1; if Race=Hispanics then d_stdrace =2, if Race=Others then d_stdrace=3
Need (during pre index period)	**NPP**	Diabetes severity-Nephropathy	(See 3.6.2. Diagnosis related variables)
	NUP	Diabetes severity-Neuropathy	
	RTH	Diabetes severity-Retinopathy	
	CO_CI	Comorbidity score based on Charlson Comorbidity index	
	CO_EI	Comorbidity index based on Elixhauser index	
	CO_CDS	Comorbidity index based on Chronic Disease Severity	
	CO_HQP	Comorbidity index based on HRQOL-CI physical aspect index	
	CO_HQM	Comorbidity	

		index based on HRQOL-CI mental aspect index	
Enabling	**D_Cap**	Type of health plan	fee-for-service=0, capitated plan=1
	D_End	Type of provider	Endocrinologist visit, d_end=1; not an endocrinologist visit, d_end=0
	Thercl_s	No. of therapeutic classes of medication	
	Rx_s	Total no. of medications	
Physician adherence to diabetes care guideline	**Pa_hbi**	Physicians' adherence to recommended no. of HbA1c test	If total no. of HbA1c test≥2, then Pa_hbi=1; otherwise Pa_hbi=0
	Pa_ldi	Physicians' adherence to recommended no. of LDL-c test	If total no. of LDL-c test ≥1, then Pa_ldi=1; otherwise Pa_ldi=0
	Pa_npi	Physicians' adherence to recommended no. of a mircoalbuminuria test	If total no. of mircoalbuminuria test ≥1, then Pa_npi=1; otherwise Pa_npi =0
	Pa_eyi	Physicians' adherence to recommended no. of eye examination	If total no. of eye examination ≥1, then Pa_eyi=1; otherwise Pa_eyi=0
	Pa_fti	Physicians' adherence to recommended no. of foot examination	If total no. of foot examination ≥1, then Pa_fti=1; otherwise Pa_fti=0
	Pasi	Physican treatment adherence score	Pasi=Pa_hbi+Pa_ldi+Pa_npi+Pa_eyi+ Pa_fti
Patient's adherence to diabetes medication	**MPR**	Medication possession ratio	(See 3.6.4. Medication related variables)
	S_a1	An indicator of whether or not	

		to switch or combine OAD	
Healthcare utilization	**Hosp_s**	Total no. of hospitalizations	
	ER_s	Total no. of emergency room visits	
	Out_s	Total no. of outpatient visits	
Healthcare costs	**Pay_ps**	Total healthcare cost in pre-index period	
	Pay_as	Total healthcare cost in post-index period	
	Pay_pds	Total diabetes care related healthcare cost in pre-index period	
	Pay_ads	Total diabetes care related healthcare cost in post-index period	

HRQL: Health related quality of life; OAD: oral antidiabetic medication; TZD: thiazolidinediones; ER: emergency room

*: the date of the first OAD prescription claim, which is the first date of the index date

Table 10 Study Variables Created from the Dataset

3.6.1. Socioeconomic Variables

The study extracted following variables from the eligibility file of the Medicaid database at the index date (the date of the first OAD prescription claim): the year of birth, gender, and race/ethnicity, healthcare insurance status, health plan, source of care, type of provider, number of medications and the frequency of medications.

Patient's age: year at the start of the first OAD therapy– the year of birth

Patient's gender: gender was classified into male or female. Gender is treated as a dummy variable, where male=0 and female=1.

Patient's race/ethnicity: race/ethnicity was recorded as White, Black, Hispanics and Others in the Medicaid database. Patient's race/ethnicity was treated as a dummy variable, where White=0, Black=1, Hispanic=2, and Others=3.

3.6.2. Diagnosis related Variables

Diagnosis codes were used to identify type 2 diabetic patients and to construct diabetes severity and comorbidity index. Diagnosis codes in the MarketScan™ database use the *International Classification of Disease, 9th Division, Clinical Modifications* (ICD-9-CM) classification system. Diagnosis codes are three to five digits in length. The first character can be alphanumeric (0-9, E or V); characters two through five are numeric or blank. Up to two diagnosis codes (DX1, DX2) are recorded on every inpatient Service record. Principal diagnosis on each record is identified as discharge diagnosis for hospital claim. Also, two diagnosis codes (DX1, DX2) are recorded on each outpatient service records.

Type 2 Diabetes

The *ICD-9-CM* codes used for identifying type 2 diabetes are 205.X0 and 250.X2.

Diabetes severity

Ideally, diabetes disease severity can be measured using clinical indicators, such as HbA1c value. However, because claim database, such as Medicaid data, does not include these clinical values, a proxy was utilized. Present study defined diabetes severity by using three diabetes related complication indicators: nephropathy, neuropathy, and retinopathy and measured these complications in pre-index period. The propensity for healthcare utilization may increase with diabetes severity. The presence of each diabetic complication was recorded as a dichotomous variable. To avoid multicollinearity the dummy variables were not summed up for each patient to obtain number of complications.

Conditions	ICD-9 or CPT code

Nephropathy	583.81X, 580.9X, 581.81, 581.9X, 582.9X, 583, 588.8X, 593.9X
Neuropathy	358.01, 354-355, 713.5X, 337.1X, 357.2X
Retinopathy	362.0X, 362.1X, 362.2, 362.41, 363.31, 369, 366.41, 365.44

Table 11 ICD-9-CM and CPT codes related to Diabetes Complications

Diagnostic-based Comorbidity score construction

Four alternative comorbidity indices will be constructed: Charlson Comorbidity index (CCI)[20], Elixhauser index (EI)[33], Chronic Disease Score (CDS)[176], and Health related Quality of Life Comorbidity index (HRQL-CI)[41]. Scores derived from the CCI, EI, and HRQL-CI indexes were based on a list of the selected ICD-9-CM diagnosis codes on inpatient, emergency room and outpatient medical claims, while the CDS was estimated utilizing the selected NDC numbers on outpatient prescription drug claims to determine prescribed drug usage. The ICD-9-CM codes for each index and NDC numbers corresponding to the drugs selected in the CDS were displayed detail in the Appendix A. We excluded the diagnostic codes of type 2 diabetes because of the disease population studied.

Regarding the time period for constructing comorbidity scores, it has been recommended that identifying diagnoses listed for a patient in prior hospitalization or the initiation of care, such as medication treatment prescribed, could improve the measurement of comorbid illnesses [38]. Comorbid illnesses may be under-reported for patients with acute conditions due to bias that favors recording secondary diagnoses associated with the cause of the acute condition over diagnoses associated with unrelated chronic illnesses [356, 357]. Some comorbid illnesses (e.g., stroke) can only be reliably measured when they are identified from prior hospitalization records, because these diagnoses represent potential complications when they occur during the index hospitalization after care is initiated, complications must be distinguished from comorbid illness when assessing outcomes of care since it is only appropriate to adjust for disorders that are present at the time of admission or before the initiation of care.

In present study, the time period for constructing comorbidity score for each patient was the time starting from the date that a patient was indentified via the diagnosis code of type 2 diabetes in the pre-index period to his or her index date, which was the first time a particular OAD was prescribed. The following described the calculation of each diagnostic-based comorbidity score in detail.

Charlson Comorbidity Index

The Charlson Comorbidity index (CCI) was originally developed for use with medical records and consisted of 19 different diseases weighted according to disease severity as 1, 2, 3, 6. Severity weights are based on the adjusted relative risks from the Cox proportional hazard regression model used in the development of the index [156]. The index has since been adapted into several 17-item weighted indexes for use with administrative data [17]. A comprehensive comparison performed by Schneeweiss et al examined differences in the predictive ability of several CCIs of mortality, long-term care admissions, hospitalizations, physician visits, and expenditures for physician services [358]. Results from that study showed little difference in the performance of different CCIs, with the adaptation by Romano et al [22] performing best. We used a modified version of the Romano-adapted Charlson index. The comorbid conditions and their corresponding original assigned weights were listed in table 12. The final CCI scores were the sum of weights assigned to all comorbidities that a patient has.

Condition	ICD-9 codes	Weight
Myocardial infarction	410, 412	1
Congestive heart failure	398, 402, 428	1
Peripheral vascular disease	440-447	1
Cerebrovascular disease	430-433, 435	1
Dementia	290, 291, 294	1
Rheumatologic disease/connective tissue disease	710, 714, 725	1
Ulcer disease	531-534	1
Mild liver disease	571-573	1
Hemiplegia	342, 434, 436, 437	2
Moderate or severe renal disease	403, 404, 580-586	2
Diabetes	------	2
Any tumor	140-195	2
Leukemia	204-208	2
Lymphoma	200, 202, 203	2

Moderate or severe liver disease	070, 570, 572	3
Metastatic solid tumor	196-199	6
AIDS	042-044	6

Table 12 ICD-9-CM Codes of Conditions and Corresponding Weights Included in the Charlson Comorbidity index

Elixhauser Index

The Elixhauser index measures the effect of 30 different comorbid conditions [33]. The index distinguishes comorbidities from complications by considering only secondary diagnoses unrelated to the principal diagnosis through the use of diagnosis related groups (DRGs). Current coding for the Elixhauser index is downloaded from the Agency for healthcare Research and Quality (table 13) [359]. The final Elixhauser scores are calculated as the sum of comorbid conditions present.

Conditions	ICD-9-CM codes
Congestive heart failure	398.91, 402.11, 402.91, 404.11, 404.13, 404.91, 404.93,428.0-428.9
Cardiac arrhythmias	426.10, 426.11, 426.13, 426.2-426.53, 426.6-426.89, 427.0, 427.2, 427.31, 427.60,427.9, 785.0, V45.0, V53.3
Valvular disease	093.20-093.24, 394.0-397.1, 424.0-424.91, 746.3-746.6, V42.2, V43.3
Pulmonary circulation disorders	416.0-416.9, 417.9
Peripheral vascular disorders	440.0-440.9, 441.2, 441.4, 441.7, 441.9, 443.1-443.9, 447.1, 557.1, 557.9, V43.4
Hypertension	401.1, 401.9, 402.10, 402.90, 404.10, 404.90, 405.11, 405.19, 405.91, 405.99
Paralysis	342.0-342.12, 342.9-344.9
other neurological disorders	331.9, 332.0, 333.4,333.5,334.0-335.9,340,341.1-341.9,345.00-345.11, 345.40-345.51, 345.80-345.91, 348.1, 348.3, 780.3, 784.3
Chronic pulmonary disease	490-492.8, 493.00-493.91, 494, 495.0-505, 506.4
Diabetes, uncomplicated	250.00-250.33,
Diabetes, complicated	250.40-250.73, 250.90-250.93
Hypothyroidism	243-244.2, 244.8, 244.9
Renal failure	403.11, 403.91, 404.12, 404.92, 585, 586, V42.0,V45.1,V56.0,V56.8
Liver disease	070.32, 070.33, 070.54, 456.0, 456.1, 456.20, 456.21

	571.0, 571.2, 571.3, 571.40-571.49, 571.5, 571.6, 571.8, 571.9,572.3,572.8, V42.7
Peptic ulcer disease excluding bleeding	531.70, 531.90, 532.70, 532.90, 533.70, 533.90,534.70,534.90, V12.71
AIDS	042-044.9
Lymphoma	200.00-202.38, 202.50-203.01,203.8-203.81, 238.6, 273.3,V10.71,V10.72,V10.79
Metastatic cancer	196.0-199.1
Solid tumor without metastasis	140.0-172.9,174.0-175.9,179-195.8, V10.00-V10.9
Rheumatoid arthritis/collagen vascular diseases	701.0, 710.0-710.9, 714.0-714.9, 720.0-720.9, 725
Coagulopathy	2860-2869, 287.1, 287.3-287.5
Obesity	278.0
Weight loss	260-263.9
Fluid and electrolyte disorders	276.0-276.9
Blood loss anemia	2800
Deficiency anemia	280.1-281.9, 285.9
Alcohol abuse	291.1, 291.2, 291.5, 291.8, 291.9, 303.90-303.93,305.00-305.03, V113
Drug abuse	292.0, 292.82-292.89,292.9,304.00-304.93,305.20-305.93
Psychoses	295.00-298.9, 299.10-299.11
Depression	300.4, 301.12, 309.0, 309.1, 311

Table 13 ICD-9 Codes of Conditions Included in the Elixhauser Index
Source: [33, 359]

Health-related Quality of Life Comorbidity Index

Health-related Quality of Life comorbidity index (HRQL-CI) consists of two lists of 20 and 15 clinical conditions for physical and mental aspects of health-related outcomes, respectively (table 14). Each condition is assigned a weight based on its relative influence on health related outcome. The final HRQL-CI physical or mental aspect of score was each the sum of weights assigned to each condition a patient present.

For physical health related outcomes			For mental health related outcomes		
Condition	**ICD-9-CM**	**Weight**	**Condition**	**ICD-9-CM**	**Weight**
Paralysis	342, 343, 344, 781.4	3	Affective Disorders, Schizophrenia,	296, 298, 300.4, 301.1, 301.3, 297,	3

			Other Psychoses	298	
Rheumatoid Arthritis and Rheumatic Disorders	714, 720	3	Anxiety, Depression	293, 300, 308, 309, 312	3
Heart Failure	415, 416, 417, 398, 428	3	HIV Infection	042-044	3
Systemic Lupus Erythematosus	710	2	Epilepsy, Convulsions	345, 780	2
Ischemic Heart Disease	411, 412, 413, 414, V458, 429	2	Hepatitis	070, 571, 573	2
Osteoarthritis/ Nontraumatic Joint Disorders	715, V134, 713, 716, 718, 719	2	Systemic Lupus Erythematosus	710	2
Hepatitis	070, 571, 573	2	Heart Failure	415, 416, 417, 398, 428	2
Diabetes	--------	2	Headaches	346, 784	1
Degenerative Neurologic Disorders	332, 325, 337, 340, 325, 332, 337, 341, 344, 347, 348, 349, 350, 351, 352 353, 354, 355, 356, 357, 358,359, 781, 782, 784,792, 730, 794, 796, V124, V415, V452, V484, V485, V493, V530	2	Biliary and Liver Disorders	574, 575, 576, 793, 570, 571, 572, 573, 782, 789, 790, 794, V427	1
Peripheral and Central Vascular Diseases	440, 443, 557, 444,445	2	Anemia	280, 281, 282, 283, 284, 285	1
Spinal Column Disorders	720, 721, 722, 723, 724	2	Gastric and Duodenal Ulcer	531, 532, 533, 534, V127, 536, 537	1
Obstructive Pulmonary	490, 491, 492, 494, 496, 495,	2	Degenerative Neurologic	332, 325, 337, 340,	1

Disease	500, 501, 502, 503, 504,505, 506, 507, 508		Disorders	325, 332, 337, 341, 344, 347, 348, 349, 350, 351, 352 353, 354, 355, 356, 357, 358,359, 781, 782, 784,792, 730, 794, 796, V124, V415, V452, V484, V485, V493, V530	
Gastric and Duodenal Ulcer	531, 532, 533, 534, V127, 536, 537	1	Diabetes	-----	1
Hypertension	401	1	Asthma	493	1
Asthma	493	1	Spinal Column Disorders	720, 721, 722, 723, 724	1
Arrhythmias	426, V450, V533, 427, 785	1			
Esophageal Disorders	456, 530	1			
Thyroid Disorders	240, 241, 242, 243, 244, 245, 246, 794.5	1			
Vision Disorders	366, V431, 367, 368,369, V410	1			
Anxiety, Depression	293, 300, 308, 309, 312	1			

Table 14 ICD-9 Codes of Conditions and Corresponding Weights Included in the HRQL Comorbidity Index
Source: [41]

3.6.3. Procedure-related Variables

Procedure codes were used to identify service-level information, including diabetes related examinations (e.g., HbAlc) and healthcare utilization (e.g.,

emergency room visits). Procedure codes in MarketScan™ database are three to five digits in length depending on the classification system used. The CPT-4 (Current Procedural Terminology, 4th Edition) coding system was the most widely used in outpatient claims. One procedure code (PROC1) is stored on each inpatient and outpatient service record.

3.6.4. Medication-related Variables

The National Drug Code (NDC) and therapeutic class (THERCLS) in the MarketScan™ database were used to identify medication prescription information, such as medication adherence and the CDS comorbidity scores.

Medication adherence

Medication adherence in this study was defined as patient's adherence to a new start of OAD medications, particularly focused on SU, MET, and TZD. Prescription refill patterns were used as a measure of adherence to index prescriptions, under the assumption that a prescription filled was a prescription taken. Pharmacy records have been demonstrated to have predictive validity as measures of cumulative exposure and gaps in medication supply

Medication possession ratio (MPR) was used to measure adherence. The observation period begins with the first date of dispensing within each year and ends as the dispensing date of the last prescription. Information on all filled prescriptions was extracted from the Medicaid claims. Each record contains information on the medication dispensed, including dosage, quantity dispensed, date of the drug supplied, and number of days supplied. During the study period, there were four fixed-dose regimens of OAD: Glucovance™ (glyburide plus metformin), Avplusamet™ (rosiglitazone plus metformin), Metaglip™ (glipizide plus metformin), and Actaoplus Met™ (pioglitazone plus metformin). Also, in order to account for difference in medication behavior between patients who used monotherapy (or fixed-dose regimen) and combined OAD treatments, we employed a dummy variable to indicate whether or not a patient switched or combined OAD

treatment during study period. Specific formulations for computing the MPR are as follows.

For monotherapy or fixed-dose regimen:

$$MPR = \frac{\text{Total days' supply obtained}}{(\text{Date of the last claim} - \text{Date of the first claim} + \text{Days' supply of the last claim})}$$

For combination therapy:

$$MPR = \frac{\text{Total days' supply obtained}/n}{(\text{Date of the last claim} - \text{Date of the first claim} + \text{Days' supply of the last claim})}$$

(n=no. of OAD combined, e.g., for dual therapy, n=2)

Prescription Claims-based Comorbidity Index: *CDS comorbidity score*

The RxRisk system [176] is a revised and expanded version of the original chronic disease score (CDS) risk assessment instrument [177]. The RxRisk is a clinically validated algorithm hat estimates expected medical care cost or the patient for the next year based on chronic disease categories and prescription drug refills. For adults, the RxRisk identified 25 distinct comorbid conditions by linking them to medications used during treatment (table 15) [176]. Weights for the RxRisk were taken directly from the originally published prospective cost coefficient estimates [177].

Chronic disease	Medication class(es)	AHFS medication category	THERCLS in MarketScan™ dataset
Anxiety and tension	Salicylate combinations, barbiturates, benzodiazepines, meprobamate, miscellaneous hypnotics, paraldehyde	Benzodiazepines, misc anxiolytics, sedative, and hypnotics	58,73, 64, 74,75,
Asthma	Anti-inflammatory glucocorticoids, isoproterenol, bronchodilators, cromolyn, xanthenes	Sympathomimetic agents, adrenals	166, 195, 138,

Bipolar disorder	Lithium	Antimanic agents	76
Cardiac disease	ClassI an antiarrhythmic, ClassI c antiarrhythmics. Class III, proccianmide, dispopyranmide, quinidine, vasodilator nitrates, diuretic loops	Cardiac drugs	49,46,120,55,48
Coronary/peripheral vascular disease	Antiplatelet, oral anticoagulants, trental	Anticoagulants, hemorrheologic agents	44,45,39,40,43
Cystic fibrosis	Anti-inflammatory glucocorticoids, enzymes	Mucolytic agents, digestants	127,158,130
Depression	Monoamine oxidase inhibitors, phenothiazine combinations,tricyclic anti-depressants, SSRIs	Antidepressants	69
Diabetes	Biguanides, insulins, sulfonylureas	----	----
Epilepsy	Anti-convulsants	Anti-convulsants	64,65,66,67,68
ESRD	Marrow stimulants, human erythropo	Hematopoietic agents	42
Gastric acid disorder	Histamine H_2 blockers, prostaglandins, proton pump inhibitor	Misc GI drugs	161,162
Gout	Colchicine, uric acid inhibitors	Unclassified therapeutic agents	234,235
Heart disease/hypertension	Beta adrenergic blockers, dopamine, calcium channel blockers	------	51,52
Hyperlipidemia	Antilipemic dofibrate, antilipidemic exchange resins, HMG coagulant reductase inhibitors	Antilipemic agent	53
Hypertension	ACE inhibitors,	Hypotensive	50,54,55,

	antihypertensive vasodilators, donidine, ganglionic blockers, guanethidine, methyldopa, rauwolfia alkaloids, alpha/beta blockers, diuretic combinations, diuretic k+ depleting agents, diuretic k+ sparing agents	agents	121,122, 123,124,125
Irritable bowel syndrome	Sulfonamide	Unclassified therapeutic agents	17
Liver disease	Ammonia detoxicants	Ammonia detoxicants	103
Malignancies	Leucovorin, monoclonal, miscellaneous antinauseants, antineoplastic alkylating, antineoplastic antibiotics, antineplastic mao inhibitors, antineoplastic progesterones, antineplastic pyrimidines, antineoplastics misc, nladder protectant, methotrexate, purine antimetabolites, colony stimulating factors	Antineoplastic agents, hematopoietic antiemetics	21,160,242
Parkinsons diseasPsychotic illnesse	Dopamine, MAOb inhibitors	Antiparkinsonian agents	25
Psychotic illness	Miscellaneous antipsychotics, butyrophenones, phenothiazines,	Tranquilizers	70

	thiothixenes		
Renal disease	Potassium removing resins	Potassium removing resins	113
Rheumatoid arthritis	Antinflammatory glucocorticoids, gold salts-injectable, gold salts-oral	Adrenals, gold compounds, antimalarial agents	163
Thyroid disorder	Thyroid replacement	Thyroid agents, antithyroid agents	178,179
Transplant	Immunosuppressive agents	Unclassified therapeutic agents	181
Tuberculosis	Anti-tuberculosis antibiotics, isoniazide	Antituberculosis agents	13
Glaucoma	Duretic carbon, anhydrase-inhibitors, ophthalmic miotics	Carbonic anhydrase inhibitors, misc EENT drugs, miotics	142
HIV	Zidovidine, didanosine, zalcitabine, pentamidine, clarithromycin, rifabantin, atovantin	Antivirals, misc. antiinfectives	14,136
Respiratory illness	Sympathomimetic agents, cromolyn	Sympathomimetic agents, mucolytics, respiratory smooth musle relaxants,	27,130,214
Migraine	Sympatholytic agents	Unclassified therapeutic agents	28

Table 15 The NDC and Corresponding Weights Included in the RxRisk system

Source: [176, 177]

3.7. Statistical Analyses

3.7.1 Statistical Analyses and Hypotheses Testing

The descriptive statistics of population characteristics were performed, including means, standard deviation, frequency and proportion. The correlations between comorbidity indexes were assessed using Spearman rank correlation, which was used to account for potential nonormality bias in the independent variables. The following statistic analyses were employed to examine the study objectives and to test study hypotheses:

Objective 1: To examine the performance of each comorbidity index in predicting physician guideline adherence, patient's medication adherence, healthcare utilizations and expenditures

Based the property of outcome variable, the predictive performance of comorbidity index was assessed through standard Poisson regression, multiple logistic regression and zero-inflated negative binomial regression models. The outcomes of study interest can be viewed as two types: count variables (physician treatment adherence score, numbers of hospitalization, outpatient visit, and ER visit) and continuous variables (medication possession ratio, total medication costs and diabetes care related costs).

For count data, the simplest and basic model is Poisson regression, which is under the critical assumption of equi-dispersion (the equality of the mean and the variance). However, in practice, many count variables have a variance greater than the mean, which is called overdispersion due to the unobserved heterogeneity and/or excess zeroes. Over-dispersion in Poisson regression will lead to deflated standard errors of parameter estimates, and therefore inflated t-statistics. Three alternative models to Poisson regression are the Negative Binomial Regression (Nbreg), Zero-Inflated Binomial Regression and Zero-inflated Poisson Regression. The Nbreg as the most common alternative to Poisson regression addresses the issue of overdispersion by including a dispersion parameter to accommodate the unobserved heterogeneity in the count data. The Nbreg can be considered a generalization of Poisson regression and assumes that the conditional mean of

dependent variable is not only determined by independent variables but also a heterogeneity component error term unrelated to independent variables. Since Nbreg is the extension of Poisson with a more liberal variance assumption and could collapsed into Poisson regression with the dispersion parameter equal to 0, this important fact provides a possibility to do the model comparison between Poisson and Nbreg, to support the evidence of appropriateness of Nbreg use alternative to Poisson model. First, t-statistics of the dispersion parameter, Alpha, assess the significance of over dispersion. Then a likelihood ratio (LR) test, which follows Chi-square distribution with 1 degree of freedom, between Poisson and Nbreg models can be used to determine the preferred model for the data. The significant LR test provides the evidence that Nbreg is preferred over Poisson regression.

However, the Nbreg is not without criticism. The inclusion of unobserved heterogeneity will increase the probabilities of both zero counts and high counts but might not yield a good fit for the distribution of count outcome with excess zeroes. Zero-inflated model, as an alternative model to handles excess zeroes, has been introduced under this consideration. A zero-inflated regression can be considered a mixture of two statistical processes, one generating zeroes counts and the other generating both zeroes and nonzero counts. More specifically, in a zero-inflated regression, a Logit model with binomial assumption is used to determine if an individual count outcome is from the always-zero or the not-always-zero group and then a model for count data, either Poisson or Nbreg, to model outcomes in the not-always-zero group. Vuong test has been a common approach to compare zero-inflated model to other non-nested models for count data, such as Poisson regression and Nbreg. Vuong specifies that the Vuong (1989) test of Zero-inflated binomial regression (Zinb) versus Nbreg be reported. This test statistic has a standard normal distribution with large positive values favoring the Zinb model (usually $V>1.96$) and large negative values favoring the Nbreg ($V<1.96$).

Therefore, considering an appropriate analysis for count data, we first described the mean and variance for a given count variable to analyze equi-dispersion property of the data. If potential over-dispersion issue is considerable (the variance greater than the mean), the Nbreg analysis was employed and two

statistic tests: (1) t-statistics of the dispersion parameter (alpha) as an indicator of over-dispersion and (2) the LR chi-square test, with degree of freedom of 1, between Poisson and Nbreg models as the determination of Nbreg model preferred to Poisson model, were carried out. If Nbreg is preferred with given evidence of significant LR chi-square test, Vuong test in the Zinb model was examined to determine whether the Zinb analysis is preferred to the Nbreg for a given count variable.

For continuous outcomes, ordinary least squares (OLS) regression was first employed and several regression diagnostics, including normality, multicollinearity, heteroskedasticity, and autocorrelation, were examined in order to ensure appropriateness of OLS regression use.

The normality of residuals (the residuals (errors) are identically and independently distributed) was examined by (1) a qqplot which plots the quantiles of residuals against the quantiles of a normal distribution and is sensitive to non-normality near the tails, and (2) Shapiro-Wilk W test for normality with insignificant testing result indicating that residual is normally distributed. The assumption of the homogeneity of variance of the residuals was checked by (1) a graphical method, which plots the residuals versus fitted (predicted) values, with no pattern to the residuals plotted against the fitted values as the evidence of homoscedasticity, and (2) the White's test for heteroscedasticity under the null hypothesis that the variance of the residuals is homogenous. The term collinearity implies that two variables are near perfect linear combinations of one another. When more than two variables are involved it is often called multicollinearity. The primary concern is that as the degree of multicollinearity increases, the regression model estimates of the coefficients become unstable and the standard errors for the coefficients can get wildly inflated. To check for multicollinearity, we employed the variance inflation factor (VIF), with a rule of thumb that a variable whose VIF values are greater than 10 may merit further investigation. The variables with very high VIF values indicate that they are possibly redundant.

The likelihood ratio (LR) for goodness of fit, deviance, adjusted pseudo R^2 were reported as statistical evidence of model fit of each model, compared to its

nested intercept only model. The LR for goodness of fit is the log likelihood ratio of the intercept-only model compared to the model with covariates. Significant LR X^2 test result indicates better model fit compared to the model without adjusted for covariates. Deviance value compares a given model to a fully saturated one. Deviance reflects error associated with the model even after the predictors are included in the model. It thus has to do with the significance of the unexplained variance in the response variable. The smaller the deviance the better the model fits the data. McFadden's pseudo R^2 is also known as the likelihood ratio index. It compares the likelihood for the intercept only model to the likelihood for the model with the predictors. The adjusted version of McFadden's R^2 subtracts K, the number of parameters in the model. Thus, the adjusted McFadden's R^2 is to McFadden's R^2 as the adjusted R^2 is to R^2 in OLS regression. This statistics indicates the level of improvement over the intercept model offered by the full model. A small ratio of log likelihoods indicates that the full model is a far better fit than the intercept model. If comparing two models on the same data, McFadden's would be higher for the model with the greater likelihood. McFadden's adjusted mirrors the adjusted R^2 in OLS by penalizing a model for including too many predictors. If the predictors in the model are effective, then the penalty will be small relative to the added information of the predictors. However, if a model contains predictors that do not add sufficiently to the model, then the penalty becomes noticeable and the adjusted R^2 can decrease with the addition of a predictor, even if the R^2 increases slightly. Therefore, adjusted R^2 value can be viewed as an informal comparison of the prediction performance to adjust for the number of explanatory variables in each regression model, and therefore could be thought of as an index value of variance that is corrected for df. The higher adjusted R^2 values correspond to improved model fit and greater predictive ability.

Since pseudo-R^2s are limited in that they can only be used to compare nested models, the Akaike's information criterion (AIC) and the Bayesian information criterion (BIC) are two common information criterion measures used to compare non-nested models. To provide a quantitative measure of model plausibility, the AIC (or BIC) difference is the difference between the AIC (or BIC) and the minimum of

AIC over all candidate models. When a zero difference in AIC value indicates the best model (serves as a reference minimum AIC value), models having ΔAIC< 2-3 are nearly tie, models havingΔ AIC between 7-10 are considered fair, and models having ΔAIC>7 -10 are substantially inferior. The criteria based on the Δ BIC is that absolute difference between the BIC and the minimum of BIC over all candidate models is "weak, positive, strong, and very strong" when the BIC difference is 0-2, 2-6, 7-10, >10, respectively.

Regarding each comorbidity index, the percent change in odds ratio of comorbidity measured by each comorbidity index was computed to indicate the impact of comorbidities (direction and magnitude). This value reflects that, for every one unit increase in comorbidity index score, percent change in expected count of outcome variable (e.g., number of hospitalization). The following specified the regression model and analysis for each outcome of interest.

For physician treatment adherence, the standard Poisson regression was selected because there was no considerable evidence of over-dispersion based on three statistical evidence (1) the descriptive result showed the variance of physician treatment adherence variable (1.237) is not greater than its mean value (2.512), and (2) insignificant Vuong test result (z =-0.17 Pr>z = 0.569) indicated that zero-inflated Poisson model is not significantly better than standard Poisson model. The regression model was as follows

[Physicians' treatment adherence]=β_0+ β_1 (predisposing factors) + β_2 (need factors) + β_3 (enabling factors) + β_4 (index year) +errors

Predisposing factors included age, gender and race. Age was entered in the regression model as a categorical variable to better understand the effect of each category on each outcome of interest. The different categories of age entered into regression were age group 18-49 years and age group 50-64 years. Need factors were 3 diabetes severity indicators (nephropathy, neuropathy and retinopathy) and comorbidity. Enabling factors were the type of health plans, type of providers, number of therapeutic classes, and number of medications. The primary independent variable of interest is comorbidity.

For patient medication adherence, which was measured by the MPR as a continuous variable, based on graphical views of MPR and its transformed products (cubic, square, sqrt and log), none of transformations and MPR has followed normal distribution. Therefore, we modeled medication adherence as a dichotomous variable by MPR ≥ 0.8 (as being in OAD medication adherence) and MPR< 0.8 (not being medication adherence) and applied logistic regression analysis. The regression model for medication adherence was as follows.

[Being in OAD medication adherence (MPR≥0.8)]=β_0+ β_1(predisposing factors)+ β_2(need factors)+ β_3(enabling factors)+ β_4(switching or combing OAD drugs (yes/no))+ β_5(index year)+errors

Predisposing, need and enabling factors were the same with factors in the model for physician treatment adherence. In addition to these factors, a dummy variable which indicated whether or not a patient switched or combined at least 2 OAD drugs was entered into the model to control for the variance in medication adherence behavior between patients who only use one type of index drug and those who either switched OAD drugs or combined at least 2 OAD. In the other words, this was an indicator of whether a patient was on an OAD monotherapy or used at least 2 different types of OAD (either switch one OAD to another or combine at least 2 different types of OAD).

For the number of hospitalization as one of healthcare related utilization of study interest, the Zinb analysis was finally selected, based on four statistical evidence: (1) the descriptive result showed the variance of the number of hospitalization variable (0.9109) was not greater than its mean value (0.3515), and (2) significant t statistics result for the dispersion parameter (alpha) (beta-coefficient:1.65, standard error:0.94, p<0.000) in Nbreg model indicated that there is significant overdispersion issue, and (3) a significant chi-square test for Likelihood-ratio between Nbreg and standard Poisson model (x^2:1278.45, df.=1, p<0.000) indicated that Nbreg is preferred to standard Poisson model, and (4) statistical significant Vuong test of Zinb versus Nbreg (z = 4.89, p= 0.0000) indicated that Zinb is preferred to Nbreg. The regression model for the number of hospitalization was as follows

[Number of hospitalization $_{\text{(in post-index period)}}$]=$\beta_0$+ β_1(predisposing factors)+ β_2(need factors)+ β_3(enabling factors)+ β_4(physician treatment adherence score)+ β_5(patient OAD medication adherence (MPR))+ β_6(switching or combing OAD drugs (yes/no))+ β_7(number of hospitalization$_{\text{(in pre-index period)}}$)+ β_8(index year)+errors

For the number of ER visit as one of healthcare related utilization of study interest, the Zinb analysis was also finally selected, based on four statistical evidence: (1) the descriptive result showed the variance of the number of ER visit variable (0.5615) was not greater than its mean value (0.2147), and (2) significant t statistics result for the dispersion parameter (alpha) (beta-coefficient:2.30, standard error:0.160, p<0.000) in Nbreg model indicated that there is significant overdispersion issue, and (3) a significant chi-square test for Likelihood-ratio between Nbreg and standard Poisson model (x^2:1121.79, df.=1, p<0.000) indicated that Nbreg is preferred to standard Poisson model, and (4) statistical significant Vuong test of Zinb versus Nbreg (z =5.2 p= 0.000) indicated that Zinb is preferred to Nbreg. The regression model for the number of hospitalization was as follows [Number of emergency room visit $_{\text{(in post-index period)}}$]=$\beta_0$+ β_1(predisposing factors)+ β_2(need factors)+ β_3(enabling factors)+ β_4(physician treatment adherence score)+ β_5(patient OAD medication adherence (MPR))+ β_6(switching or combing OAD drugs (yes/no))+ β_7(number of emergency room visit $_{\text{(in pre-index period)}}$)+ β_8(index year)+errors

For the number of outpatient visit as one of healthcare related utilization of study interest, the Zinb analysis was also finally selected, based on four statistical evidence: (1) the descriptive result showed the variance of the number of outpatient visit variable (1402.656) was not greater than its mean value (27.434), and (2) significant t statistics result for the dispersion parameter (alpha) (beta-coefficient: 0.401, standard error:0.0064, p<0.000) in Nbreg model indicated that there is significant overdispersion issue, and (3) a significant chi-square test for Likelihood-ratio between Nbreg and standard Poisson model (x^2:85000, df.=1, p<0.000) indicated that Nbreg is preferred to standard Poisson model, and (4) statistical significant Vuong test of Zinb versus Nbreg (z =6.95 p= 0.000) indicated that Zinb is

preferred to Nbreg. The regression model for the number of hospitalization was as follows

[Number of outpatient visit $_{\text{(in post-index period)}}$]=$\beta_0$+ β_1(predisposing factors)+ β_2(need factors)+ β_3(enabling factors)+ β_4(physician treatment adherence score)+ β_5(patient OAD medication adherence (MPR))+ β_6(switching or combing OAD drugs (yes/no))+ β_7(number of outpatient visit $_{\text{(in pre-index period)}}$)+ β_8(index year)+errors

For total medication costs and diabetes care related costs as outcome variables, the data were considerably skewed to right. Log-linear and generalized linear models (GLMs) are two commonly used methods of analyzing healthcare expenditure data, particularly for dealing with skewed data. Manning and Mullahy [360] describe the criteria necessary for choosing between the two. The Park test, which is applied for family selection in a GLM [360], indicating that a GLM model with gamma family was most appropriate for this analysis the regression models for each types of medical costs were as follows.

[Total medical costs $_{\text{(in post-index period)}}$]=$\beta_0$+ β_1(predisposing factors)+ β_2(need factors)+ β_3(enabling factors)+ β_4(physician treatment adherence score)+ β_5(patient OAD medication adherence (MPR))+ β_6(switching or combing OAD drugs (yes/no))+ β_7(total medical costs $_{\text{(in pre-index period)}}$)+ β_8(index year)+errors

[Diabetes care related costs $_{\text{(in post-index period)}}$]=$\beta_0$+ β_1(predisposing factors)+ β_2(need factors)+ β_3(enabling factors)+ β_4(physician treatment adherence score)+ β_5(patient OAD medication adherence (MPR))+ β_6(switching or combing OAD drugs (yes/no))+ β_7(diabetes care related costs $_{\text{(in pre-index period)}}$)+ β_8(index year)+errors

Bayesian and Akaike's information criteria (BIC and AIC, respectively), log-likelihood scores, R^2 statistics and pseudo For each outcome variable, the AIC was applied to the 4 separate models, each using a different comorbidity index (CCI, EI, CDS, HRQL-CI) as a predictor variable, and the model with the lowest AIC was selected as the best model. AIC is computed from the log likelihood of a model and the number of parameters in a model. In general, the rule of thumb for identifying a model or a set of models as "better" is a difference in AIC values > 4 between models. R^2 values were calculated to determine the best fit statistically. R^2 statistics was

used to reflect the proportions of explained variance, while pseudo R^2 values are the percentage reeducation of log-likelihood values from the fully restricted model (model with no covariates) to the models in question (model with one more covariates).

Objective 2: To examine the discriminative validity of comorbidity index in demographics, healthcare related behavior, utilization and expenditures

The c statistics quantifies the area-under-the-Receiver Operator Characteristic (ROC) curve was employed for the purpose of this objective. The ROC is a measure of the discriminative ability of an event or outcome (a dichotomous criterion standard outcome). The y axis on the ROC curve represents the sensitivity of a measure (true positive rate), which is the percentage of people with a measure score greater than a selected cut-off point among those with the outcome of interest (e.g., those with the health-related quality of life score greater than 50 points) or the percentage of people being experienced an event of interest (e.g. death). The x axis on the ROC curve represents one minus the specificity of a measure (false-positive rate), which is the percentage of people with a measure score greater than a selected cut-off point among those without an event of interest (e.g., death). The area under the ROC curve (called, c statistic) is the sensitivity of a measure against one minus the specificity of a measure. The c statistic represents the overall probability that a measure classifies people accurately based on an external or objective criterion with a selected cut-off point (a dichotomized point). Values of the c statistic range from 0 to 1, with 1 indicating perfect prediction and 0.5 being chance prediction; values greater than 0.7 indicate acceptable prediction; greater than 0.8, excellent prediction [361].

In present study, the extent to which a comorbidity index can accurately differentiate six types of dichotomized subgroups, including: (1) 2 age subgroups based on a age cutoff of 50 years: Older (50-64 years) versus Younger (18-49 years), (2) 2 racial subgroups: White versus non-White (including Black, Hispanic and Others as defined in the MarketScan™ dataset), (3) 2 groups classified using a cutoff of physician treatment adherence score of 4: Better treatment (score≥4) versus

Poor treatment (score<4), (4) 2 groups classified using a cutoff of the MPR value of 0.8: medication adherent (MPR≥0.8) versus non-adherent (MPR<0.8) (5) subgroups varying in healthcare related utilization: Higher users (visits≥ 90th percentile of visits among study population) versus Lower users (visits< 90th percentile), (6) subgroups varying in healthcare expenditures: High spending (costs ≥ 90th percentile of costs among study population) versus Low spending (costs< 90th percentile)

To compare discriminating abilities of comorbidity indexes, Delong et al's (1988) methods for correlated ROC curves comparison[362] were applied using the ROC and ROCCONTRAST statements in PROC LOGIST procedure in SAS software version 9.2[363]. We chose the CCI as the reference index for the purpose of two indexes comparison because it is most widely used comorbidity measure. Data files were identified and available to the researcher in SAS format. Data management and analysis was conducted using SAS software version 9.2.[363]

Objective 3: to investigate the dimensionality of comorbidity candidates from the HRQL-CI and compare our proposed comorbidity dimensional structure based scores with the commonly used approach of a single summative comorbidity score

With considering the evidence that the presence of comorbidities varied in gender and race and as such contributed to the gender and racial disparities among diabetes patients,[364-366] we stratified study population by gender and race, in order to identify the patterns of comorbidities specific to these demographic subgroups. The following three analytical steps were performed within each subgroup.

1. **Assessment of dimensionality of comorbidities**

To assess comorbidities structure, confirmatory factor analysis (CFA) in the LISREL computer program (version 8.80; Scientific Software International Inc, Lincolnwood, III) was used as a mean to explore the correlations (i.e., patterns of comorbidity) among variables (i.e., comorbidities) by postulating that these

correlations arose because of the influence of a smaller number of underlying, latent dimensions.

Specifically, tetrachoric correlation matrices created by the computer program PRELIS (version 2.2; Scientific Software International Inc, Lincolnwood, III), was assessed to obtain a preliminary understanding of how the individual comorbidities grouped together. The correlation matrices, together with clinical judgments by investigators, provided an aid in grouping comorbidities for the purpose of the CFA. Then, tetrachoric correlation matrices and asymptotic covariance matrices computed by the PRELIS were used as input data in the CFA analyses.

Three types of comorbidity structure models were evaluated using the CFA. First, 1-factor model (uni-dimensional model) was evaluated in which all comorbidities were presumed to be indicators of a single, unitary propensity to experience comorbidities. Second, based on the original HRQL-CI index, which consists of physical and mental sub- parts of indexes, a 2-factor model was evaluated in which 15 comorbidities were presumed to reflect physical domain of comorbidities, and 10 comorbidities were presumed to reflect mental domain of comorbidities. This model was inspired by the concept that that the impacts of physical and mental illness burden on health outcomes can be differential. Third, a multiple dimensional model was evaluated in which the dimensions/factors were formed based on the correlation matrices and clinical judgements.

For each study subgroup, three competing CFA models (1, 2, multi-dimensional models) were assessed using the LISREL and compared. The model parameters were estimated using weighted least squares, a procedure that requires the aforementioned asymptotic covariance matrices. The weighted least squares procedure is appropriate for the analysis of patterns of comorbidity among the HRQL comorbidities because, it does not assume that the measured variables (i.e., comorbidities) have a joint multivariate normal distribution in the population. The fit of the models was evaluated using multiple fit indices: the X^2 goodness of fit statistic, the root mean square error of approximation (RMSEA), standardized root mean residual (SRMR), comparative fit index (CFI), and Akaike's Information

Criterion (AIC). Each of these indices is commonly reported in CFA analyses, and each provides a complementary perspective on the fit of a CFA model. The X^2 value for a model indexes the discrepancy between the model-estimated and sample-derived correlations; smaller values result from better-fitting models. The RMSEA values of less than .08 were viewed as reflecting an adequate fit, with values less than .06 representing an excellent fit.[367] The SRMR indexes how far off the model-estimated correlations are from sample-derived correlations (on average) and hence should be small for well-fitting models. [368] The CFI values close to one indicate good fit and the values around 0.9 indicate acceptable fit. There are no absolute cutoff on the AIC, but this index can be used to compare models, with lower values representing better fit.[369, 370] Conventional guidelines suggest that a difference of <6 in the AIC values between two models (either nested or non-nested)is small, 6–10 is substantial, and >10 is very substantial.[370]

2. **Construction of comorbidity scores**

Based on a uni-dimensional model, two types of scores were estimated: a simple count summative score and empirically driven weight summative score. A simple count summative score was calculated by summing the presence of comorbidity candidates a person has. To obtain empirically driven weight summative score, we randomized study sample into two halves. Empirically driven weights were estimated based on strength of regression coefficient of individual comorbidity candidate for a given healthcare outcome from a half of study sample. Then, these empirically driven weights were applied into another half sample to obtain a summative weighted score by summing weights for comorbid conditions a person has.

Based on a two-dimensional model, three types of scores were estimated. Like the uni-dimensional model, we computed a simple count summative and empirically driven weight summative scores for each of two dimensions. Moreover, we computed a point weight summative score where the weights were originally assigned in the HRQL-CI index. A point weight score was estimated by summing point weights for comorbid conditions a person has.

Regarding the multi-dimensional comorbidity structure, we treated each dimension as a separate variable so one's illness burden was represented by a set of individual comorbidity scores, rather than a single summative score. For each comorbidity dimension, we had two types of scoring: a simple count score and factor loading based weight score. For a simple count score, each comorbidity dimension was treated as a dichotomous variable where a person having at least one comorbidity indicator for a given dimension was recorded as 1 and a person with no comorbidity indicator for that dimension was recorded as 0. Moreover, we used factor loading as a weight for each comorbidity indicator. For a given comorbidity dimension, factor loading based weight score was the average of factor loadings for comorbidity indicators a person has.

3. Predictive performance of competing comorbidity models

To assess the performance of comorbidity scores based on three comorbidity structures in predicting healthcare behaviors, utilization and costs, statistical analyses performed were same procedures as those used in study aim 1 for assessing predictive performance of comorbidity measures.

Specifically, physician treatment adherence score, as a count variable, were modeled using standard Poisson regression model. We modeled medication adherence as a dichotomous variable based on a cutoff of the MPR values as 0.8 (MPR ≥ 0.8: being in adherent; MPR< 0.8: not adherent) and applied logistic regression analysis. In addition to comorbidity as independent variable of interest, the covariates in the models for physician and patient's adherence behaviors were predisposing and enabling factors, and three diabetes severity indicators. Zero-inflated binomial regression analysis was applied for each type of healthcare utilization data in post index period. Medical expenditure data were considerably skewed to right. Log-linear and generalized linear models (GLMs) are two commonly used methods of analyzing healthcare expenditure data, particularly for dealing with skewed data. Manning and Mullahy [360] describe the criteria necessary for choosing between the two. The Park test for family selection in a GLM [360] indicated that a GLM model with gamma family was most appropriate for this analysis. The covariates in the models for healthcare utilization (or costs) outcome

data were predisposing, enabling and need factors, healthcare related behaviors (physician treatment adherence and patient medication adherence), and healthcare utilization (or costs) in pre-index period.

The likelihood ratio (LR) for goodness of fit, deviance and adjusted pseudo R^2 were also reported as statistical evidence of model fit of each model, compared to its nested intercept only model. The LR for goodness of fit is the log likelihood ratio of the intercept-only model compared to the model with covariates. Significant LR X^2 test result indicates better model fit compared to the model without adjusted for covariates. Deviance value compares a given model to a fully saturated one and reflects error associated with the model even after the predictors are included in the model. The smaller the deviance the better the model fits the data. McFadden's pseudo R^2, known as the likelihood ratio index, compares the likelihood for the intercept only model to the likelihood for the model with the predictors. Adjusted McFadden's R^2 subtracts K, the number of parameters in the model. Adjusted McFadden's R^2 is to McFadden's R^2 as the adjusted R^2 is to R^2 in OLS regression. Higher adjusted R^2 values correspond to improved model fit, greater predictive ability. The Akaike's information criterion (AIC) and Bayesian information criterion (BIC) are two common information criterion measures used to compare non-nested models and the model with the lowest AIC or BIC value is the best model.

3.8. Data Management and Analysis

Data files were identified and available to the researcher in SAS format. Data management was conducted using SAS software version 9.2 [363]. For the purpose of analyses, data were converted into STATA software format version 11.0 [371]. Confirmatory factor analysis was carried out using the LISREL computer program (version 8.5; Scientific Software international).

Chapter

4. Dissertation Manuscript 1: Title: Assessment of Predictive Validity of Comorbidity Indexes in Health related Behaviors and Outcomes in Medicaid Enrollees with Type-2 Diabetes

Abstract:

Background: Controlling for differences in comorbidity is particularly important in epidemiological, outcome, and health services research. Although the Charlson Comorbidity Index (CCI), Elixhauser Index (EI), Chronic Disease Score (CDS), and Health related Quality of Life Comorbidity Index (HRQL-CI) have been validated individually, no direct comparison researches in predictive performance among these alternative indexes in Medicaid diabetes patients.

Objective: To assess and compare the CCI, EI, CDS, and HRQL-CI in predicting healthcare related behaviors (, physician treatment adherence and patient medication adherence) and outcomes (, healthcare utilization and expenditures).

Methods: Using the MarketScan™ Medicaid database from 2003 to 2007, type 2 diabetes patients were targeted. Physician adherence scores were modeled using standard Poisson regression. Dichotomized medication adherence outcome variable was modeled using logistic regression. Healthcare utilization data were analyzed using zero-inflated binomial regression. Healthcare costs were analyzed by generalized linear regression. The SAS and STATA soft wares were used for data management and analysis.

Results: 9,832 patients were included, with mean age of approximate 45 years and majority of population was female (73%) and White (52%). The results showed that the CDS had best performance in predicting physician adherence. The CDS and HRQL-CI mental aspect index had better predictive validity for medication adherence behavior but each had different direction of impact: the CDS scores, as representing overall illness profile, was positively related to medication adherence,

while the HRQL-CI mental aspect of index as the index specific to mental illness showed negative impact. Diagnosis-driven indexes (e.g., CCI and EI) had better performance in predicting healthcare related utilization and expenditures.
Conclusion: In populations with chronic diseases, for studying healthcare related behaviors, the CDS and HRQL-CI mental aspect index could be relatively better risk adjustment tools and diagnosis-driven indexes could be the first choice for healthcare utilization and expenditures data.

Introduction

Comorbidity refers to any distinct additional entity that has existed or may occur during the clinical course of a patient who has the index disease under study. [7] It has been shown that 57 million Americans had multiple chronic conditions in 2000 and that this number will rise to 81 million by 2020 [1], with a consistent trend worldwide [2-6]. The role of comorbidities in the healthcare system has been an intense area of investigation, due to the awareness of their impact on many facets of healthcare outcomes, including mortality, healthcare utilization and costs.[8-15]

Since there is no gold standard approach to measure comorbidity, many alternative measures exist in the literature. The Charlson Comorbidity Index (CCI) [17], Elixhauser Index (EI) [33] and Chronic Disease Score (CDS) [35] are three commonly used comorbidity indexes. The CCI and EI can be viewed as disease diagnosis-derived measures and often used by the investigators who primarily targeted mortality or healthcare utilization as the outcomes of interest [36-38]. The CDS based comorbidity score is based on a list of medications, which represent patient's underlying disease status, and it has been demonstrated better predictive ability in healthcare expenditures, compared to diagnosis-derived indexes.[32, 39] The Health related Quality of Life Comorbidity Index (HRQL-CI) was a newer diagnosis-derived measure that was originally predictive of HRQL as measured by the SF-12 PCS (physical component summary score) and MCS (mental component summary score) using the Medical Expenditure Panel Survey (MEPS) database.[41]

However, there is no gold standard for assessing comorbidity because the predictive performance of individual comorbidity measure varies in the context of study population and outcome of interest. [32] In this regard, investigators should choose comorbidity indices appropriate to both their study population and outcome of interest.[33] Although the CCI, EI, and CDS, and HRQL-CI have been validated individually, it is important to examine relative predictive performances of these alternative measures in the context of specific settings, population and health outcomes. Moreover, most previous research have focused on assessing comorbidity impact on mortality[37, 38, 358, 372-374] and healthcare

utilization[174, 358, 374] and costs[157, 358, 375], while healthcare related behaviors, such as physician treatment and patient medication-taking behaviors, were lack of research attention.

Diabetic patients in Medicaid population could serve an ideal candidate for comorbidity research. Medicaid beneficiaries are unique in terms of comorbidity research because Medicaid settings comprise of a vulnerable population affected by multiple medical conditions.[42] Also, as diabetic patients, multiple medical conditions often occur on their clinical course of diabetes prognosis. [6, 50-53] Moreover, healthcare related outcomes among diabetes patients have been found affecting by other comorbid conditions profoundly.[8]

Therefore, the present study undertakes the aim to investigate comparative predictive performances among existing alternative comorbidity indexes across a spectrum of health outcomes. Understanding predictive performance of existing comorbidity measures is critical. In clinical perspective, a predictive valid comorbidity index could serve as a prognostic indicator to assist practitioners predicting patient's disease prognosis and identifying patients at highest risk of premature disability and death. For healthcare policymakers, to allocate medical resource more efficiently and to minimize potential economic crisis, a valid comorbidity index could serve as a forecasting tool to identify patients at risk of high health care demands or being economic burden. To our knowledge, this is the first study to compare predictive performance of comorbidity indexes exhaustively across healthcare related behaviors.

Method:

Data source

This retrospective, observational, cohort study used the data from Thomson's MarketScan™ Medicaid dataset[355] from 2003 to 2007. The MarketScan™ Medicaid dataset is a widely used source of data for many studies in different disease areas. It represents eight states of varying sizes across the United States. The database includes healthcare coverage eligibility and service use of

individuals enrolled in state Medicaid programs from eight states. It includes outpatient and inpatient services, prescription drug claims, long-term care, and enrollment data. In addition to standard demographic variables such as age and gender, the database also includes variables such as ethnicity, Medicare eligibility, and provider specialty.

We further classified study period into three specific intervals: (1) index drug identification period was the time window from 2004 to 2006. Within 24 months, the date when a patient's first OAD prescription claim occurred was defined as index date and the drug of the first OAD prescription is defined as index prescription. (2) Pre-index period was 12 months prior to the index date (starting from a patient's index date and look-back in time up to 12 months) and was used to verify continuous Medicaid eligibility as well as to identify baseline characteristics before starting any therapies. This also helped determine patients who did not have any OAD claims in this period and confirm a new start of the OAD medications in the index date. (3) Post-index period was12months after the index date (starting from a patient's index date and look-forward in time up to 12 months) and was used to ensure that patients had at least 12 months of follow-up period. Healthcare related behaviors (e.g., medication taking behavior) and outcomes (e.g., costs) were examined in this period.

Sample selection criteria

In the MarketScan™ database, individuals who satisfied all six following criteria were included in study cohort. (1) At least one outpatient or inpatient diagnosis of type 2 diabetes diagnosis based on the International Classification for Disease Code-9th revision Clinical Modification, ICD-9-CM=250.0x-250.9x, where x=0 or 2. (2) Aged 18 to 64 years old at the index date. The reason for excluding individuals aged 65 years and above was that these people may be dual beneficiaries (Medicare and Medicaid enrollees) and therefore obtaining complete data on these patients may not be available. (3) Continuous enrollment in Medicaid in the pre- and post-index periods. The continuous enrollment criterion ensures that all study subjects had the same follow-up period, and therefore reduces bias due to failure to follow-up. (4) At least one filled prescription for OAD. (5) Drug naïve

patients in pre-index period and newly starting OAD medication therapy during the index period window (2004-2006). Considering that newly treated patients beginning their first course of medication are likely to have different medication use behaviors and responses to medication than are those already on a particular therapy, only newly started cases were included to understand the medication use behavior based on individuals who are naïve to OADs. (6) Patients with continuous medication therapy was defined by 2 following criteria: (a) Therapy without a lapse of> 60 days between date of days' supply expiration of any prescription fill and the subsequent claim date (days between end date of first fill and date of next fill), and (b) At least 2 prescription on the index medication.

Study variables

We focused on two aspects of outcomes, including healthcare related behaviors and outcomes. As guided by the Aday-Anderson's model for health care service utilization[64], three types of predictors for health outcomes were identified, including predisposing, enabling and need factors.

First, healthcare related behaviors were measured in post-index period. Two types of healthcare related behaviors of study interest were physicians' adherence with diabetes treatment guideline and patient OAD medication adherence.

Physician's treatment compliance score was based on five recommended examinations by the American Diabetes Association (2005) [204], including at least two hemoglobin tests (HbA1c) per year, a cholesterol test per year, an eye examination per year, a mircoalbuminuria test per year and a foot examination per year. The final score was calculated as the sum of the number of recommended procedures completed. A person receiving more than 2 HbA1c tests was only given credit for it once. Except for the HbA1c test, a person having the same examination multiple times in the allotted time (e.g., more than one cholesterol screening within one year) was only given credit for it once. Treatment adherence scores range from zero (no recommended procedures performed) to five (all recommended procedures provided).

Medication adherence in this study was defined as patient's adherence to a new start of OAD, particularly focused on 3 common OAD as index drugs, including

sulfonylureas, metformin, and thiazolidinediones and their fixed-dose regimens, which were available in our study period, including Glucovance™ (glyburide plus metformin), Avplusamet™ (rosiglitazone plus metformin), Metaglip™ (glipizide plus metformin), and Actaoplus Met™ (pioglitazone plus metformin). Prescription refill patterns were used as a measure of medication adherence under the assumption that a prescription filled was a prescription taken. Medication possession ratio (MPR) was used to measure adherence. The observation period begins with the first date of dispensing (index date) and ends as the dispensing date of the last prescription within post-index period. Information on all filled prescriptions was extracted from the pharmacy claims file in MarketScan™ Medicaid data. The formulations for computing the MPR were as follows. For monotherapy or fixed-dose regimen: MPR=total day's supply obtained/(date of the last claim—date of the first claim+day's supply of the last claim); for combination therapy (e.g., using more than one types of index drug or switching drugs): MPR=total day's supply obtained/n*(date of the last claim—date of the first claim+day's supply of the last claim) (n=no. of OAD combined, e.g., for dual therapy, n=2)

Second, healthcare related outcomes, including healthcare utilization and costs, were measured for both pre-and post-index periods. Healthcare utilization included total number of hospitalizations, emergency room and outpatient visits. Healthcare costs included total healthcare cost and diabetes care related costs

Third, three aspects of predictors of health outcomes were predisposing, need and enabling factors. Predisposing variables were patient's age, gender and race/ethnicity. Enabling variables included three aspects of factors**:** access-related variables: healthcare insurance status and type of health plan, provider-related variables: type of provider (general practitioner vs. endocrinologist), and medication-related variables: number of therapeutic classes and total number of drugs.

Need variables included diabetes disease severity and comorbidity. We defined diabetes severity using 3 diabetes related complications as indicators: nephropathy, neuropathy, and retinopathy, and measured these complications in

pre-index period. The propensity for healthcare utilization may increase with diabetes severity. The presence of each diabetic complication was recorded as a dichotomous variable. To avoid multicollinearity the dummy variables were not summed up for each patient to obtain number of complications. Four alternative comorbidity index scores were constructed: Charlson Comorbidity index [20], Elixhauser index [33], Chronic Disease Score [176], and Health related Quality of Life Comorbidity index [41]. Scores derived from the CCI, EI, and HRQL-CI indexes were based on a list of the selected ICD-9-CM diagnosis codes derived from inpatient, emergency room and outpatient medical claims, while the CDS was estimated utilizing the selected National Drug Code (NDC) numbers from outpatient prescription drug claims to determine prescribed drug usage.

Statistical analysis

Descriptive statistics of population characteristics were performed, including means, standard deviation, frequency and proportion. The correlations between comorbidity indexes were assessed using Spearman rank correlations.

Predictive validity of comorbidity indexes for healthcare outcomes was assessing using multiple regression techniques, with controlling for three aspects of predictors (predisposing, need and enabling factors) based on the Aday-Anderson's model for health care service utilization[64]. Specific regression analyses were chosen based on the property of outcome data. Physician treatment adherence score, as a count variable, were modeled using standard Poisson regression model. We modeled medication adherence as a dichotomous variable based on a cuff off of the MPR values as 0.8 (MPR ≥ 0.8: being in adherent; MPR< 0.8: not adherent) and applied logistic regression analysis.

[Physician's treatment guideline adherence score]= β_0 + β_1 [predisposing factors] + β_2 [need factors] + β_3 [enabling factors] + β_4 [index year]+errors

[MPR ≥ 0.8: being in medication adherence]= β_0 + β_1 [predisposing factors] + β_2 [need factors] + β_3 [enabling factors] + β_4 [index year] + β_5 [whether or not switching or combining OAD (yes/no)]+errors

Zero-inflated binomial regression analysis was applied for each type of healthcare utilization data in post index period. Medical expenditures data were considerably skewed to right. Log-linear and generalized linear models (GLMs) are two commonly used methods of analyzing healthcare expenditure data, particularly for dealing with skewed data. Manning and Mullahy [360] described the criteria necessary for choosing between the two. The Park test for family selection in a GLM [360] indicated that a GLM model with gamma family was most appropriate for this analysis. The covariates in the models for healthcare utilization (or costs) outcome data were predisposing, enabling and need factors, healthcare related behaviors (physician treatment adherence and patient medication adherence), and healthcare utilization (or costs) in pre-index period.

[No. of healthcare utilization$_{\text{(post-index time)}}$]= β_0 + β_1 [predisposing factors] + β_2 [need factors] + β_3 [enabling factors] + β_4 [index year] + β_5 [physician treatment guideline adherence score]+ β_6 [OAD medication adherence (MPR)] + β_7 [whether or not switching or combining OAD (yes/no)] + β_8 [No. of healthcare utilization$_{\text{(pre-index time)}}$]+errors

(three types of healthcare utilization data, including hospitalization, emergency room visit and outpatient visit, were analyzed as outcome variable separately.)

[No. of healthcare costs$_{\text{(post-index time)}}$]= β_0 + β_1 [predisposing factors] + β_2 [need factors] + β_3 [enabling factors] + β_4 [index year] + β_5 [physician treatment guideline adherence score]+ β_6 [OAD medication adherence (MPR)] + β_7 [whether or not switching or combining OAD (yes/no)] + β_8 [No. of healthcare costs$_{\text{(pre-index time)}}$]+errors

(two types of healthcare costs data, including total medical cost and diabetes care related costs, were analyzed as outcome variable separately.)

The likelihood ratio (LR) for goodness of fit, deviance and adjusted pseudo R^2 were reported as statistical evidence of model fit of each model, compared to its nested intercept only model. Two common information criterion measures, the Akaike's information criterion (AIC) and Bayesian information criterion (BIC), were

used to compare non-nested models and the model with the lowest AIC or BIC value is the best model.

Data files were identified and available to the researcher in SAS format. Data management was conducted using SAS software version 9.2 [363]. For the purpose of analyses, data were converted into STATA software format version 11.0 [371].

Results

Characteristics of study population

The descriptive results for the 9,832 individuals who comprised our study cohort are as summarized in table 16. Study population were on average age of 44.81 (±11.64) years old and majority of population was female (73%), White (52%), on Fee-For-Service plan (55%) had took average 11 (±10.82) different types of therapeutic classes of medications and average 557(±48.64) drugs during pre-index period, 2% of individuals with nephropathy, 5% of individuals with neuropathy and 2% of individuals with retinopathy. Mean scores ranged from 0.709 (±1.27) for the CCI, 1.73 (±1.55) for the EI, 4.64 (±2.96) for the CDS, and 4.15 (±3.69) and 3.65 (±3.39) for HRQL-CI physical and mental aspects of indexes, respectively.

Over half of population had at least twice HbA1c test, one LDL-c test, and one eye examination per year (70.69%, 63.15% and 43.70% for HbA1c, 1 LDL-c, and eye examination, respectively), while less one quarter of population had at one nephropathy screening per year an very few patients had at least one foot examination. The average of physician treatment adherence score was 2.51 (±1.11). Average MPR was 0.81 (±0.26). Average MPR for patients with switching or combination regimens was higher than patients on monotherapy or fixed-dose regimens (MPR: 0.95, 0.775, and 0.783 for switching/ combination regimens, monotherapy, and fixed-dose regimens, respectively). Within patients on monotherapy, those treated by TZD had highest average MPR (MPR: 0.81, 0.77, and 0.70 for TZD, Sulfa and Met, respectively).

Regarding healthcare utilization, average number of outpatient visit tended to be higher than hospitalization and emergency room visit. Average number of

outpatient visit for a patient in pre-and post-index periods were 24.47 (±14.85) and 27.43 (17.45), respectively. Average number of hospitalization for a patient in pre- and post-index periods were 0.38 (±0.09) and 0.35 (±0.096), respectively. Average number of emergency room visit for a patient in pre-and post-index periods were 0.23 (±0.09) and 0.21 (±0.74), respectively. For medical expenditures, average total medical costs for a patient in pre-and post-index periods were 8,318.34 (±24,051) and 8,807.67 (±27,204), respectively, while diabetes care related costs for a patient were 1,282.93 (±8,381) and 2,257.99 (±9,968), respectively.

Correlations of Comorbidity Indexes

The strength of the correlations between the different indexes varying across types of measurements was given in table 17. The correlations between any two of the ICD-9-CM claims-based indexes (the CCI, EI and HRQL-CI physical and mental aspects of indexes) are fair ($\rho>0.5$), with one exception of small correlation between the CCI and HRQL-CI mental aspect of index ($\rho=0.39$). In addition, there are fair correlations between any one of the ICD-9-CM claims-based indexes and the pharmacy claims-based index (the CDS), with one exception of slightly low correlation between the CCI and CDS ($\rho=0.41$).

Predictive Validity of Comorbidity Indexes in Healthcare related Behaviors

The results regarding the predictive performance of comorbidity indexes in healthcare related behaviors were as summarized in table 18. Regarding the prediction in physician treatment adherence, the model with CDS comorbidity scores had better model fit, with given evidence of smallest deviance, AIC and BIC values, and largest adjusted pesudo-R^2. According to the model with CDS comorbidity scores, every one-unit increase in the comorbidity score, the expected physician treatment adherence score statistically significant increases by 1.7%, holding other covariates in the model constant.

To predict patient medication adherence, the HRQL-CI mental index based model has the best model fit, based on the evidence of the smallest AIC and BIC. The difference in the AIC (ΔAIC) between the HRQL-CI mental index and CDS based models was close to 3, indicating that these two index based models were tied. However, ΔAIC between the HRQL-CI mental index and CCI, EI, or HRQL-CI physical

index based model was over 7, implying that these indexes based models is each substantially inferior than the HRQL-CI mental index based model.

Comorbidity scores measured by the CDS or HRQL-CI-mental aspect of index were statistically significant associated with OAD medication adherence. However, each of them indicated different direction comorbidity impact on the medication adherence. With one unit increase in CDS comorbidity scores, the probability of being adherent increases by 3.72%, while with one unit increase in the mental aspect of HRQL-CI scores, the probability of being adherent decreases by 2.49%.

Predictive Validity of Comorbidity Indexes in Healthcare Utilization

The results regarding the predictive performance of comorbidity indexes in healthcare utilization were summarized in table 19. To predict hospitalization and ER visits, the models adjusting diagnosis-based comorbidity scores (CCI and EI) demonstrated better model fit compared to medication-based comorbidity scores (CDS), with the evidence of smallest deviance, AIC and BIC values and largest adjusted pesudo-R^2. Because Δ AIC (or Δ BIC) between the CCI and EI based models was close to 3, these two diagnosis-based comorbidity models were tied. However, ΔAIC (or ΔBIC) between the CCI (or EI) and CDS- based models were over 10, implying that the model adjusting for medication-based comorbidity scores was substantially inferior than ones adjusting for diagnosis-based scores. According to the models with EI comorbidity scores, for every one-unit increase in the comorbidity score, the expected number of hospitalization increases by 10.23% and the expected number of emergency room visit increases by 9.5%, holding other variables constant ($p<0.001$).

To predict outpatient visits, the model with HRQL-CI mental aspect comorbidity scores had the best model fit, with the evidence of smallest deviance, AIC, and BIC values, and largest adjusted pesudo-R^2. According to the models with HRQL-CI mental aspect comorbidity scores, for every one-unit increase in the comorbidity score, the expected number of outpatient visit increases by 5.3%, holding other variables constant ($p<0.001$).

Predictive Validity of Comorbidity Indexes in Healthcare Expenditures

The results regarding the predictive performances of comorbidity indexes in healthcare expenditures were given in table 20. Overall, the models with EI comorbidity scores had better model fit in predicting both total and diabetes care related costs. According to the models with EI comorbidity scores, for every one-unit increase in the comorbidity score, the expected total medical costs increases by 15.3% and the expected diabetes care related medical expenditures increases by 28.67%, holding other variables in the model constant ($p<0.001$).

Discussion

To our knowledge, this is the first study to compare predictive validity of alternative comorbidity measures exhaustively across a spectrum of critical healthcare outcomes in Medicaid diabetic patients. Our results demonstrated the comparative performances of comorbidity indexes for healthcare related behaviors and outcomes and suggested most valid risk adjustment tool for a given healthcare outcome.

Specifically, first, we demonstrated comparative predictive performances of alternative comorbidity indexes for a given healthcare outcomes and relative predictive abilities of individual comorbidity index across different healthcare outcomes. Our findings suggest that the selection of comorbidity index should be specific to a given healthcare outcome because the predictive ability of comorbidity index varied in the context of outcome of interest.

Second, in Medicaid population with diabetes disease, our findings suggested potential most valid risk adjustment tool to control for the effect of comorbidities on a given outcome of interest and revealed the direction and magnitude of comorbidity impact. For the outcome of physician treatment guideline adherence, the CDS could be the most appropriate risk adjustment tool, compared to the CCI, EI and HRQL-CI. According to CDS comorbidity scores, comorbidities exerted positive impact on physician behavior, which supported previous findings that diabetic patients with more comorbid burden were more likely to receive recommended care.[268-270] Potential explanation is that patients with multiple conditions might

receive a greater number of clinic invitations, have more frequent attendance and enhanced management as they will be on multiple diseases registers.

To analyze medication adherence outcome, the CDS and HRQL-CI mental aspect index could be appropriate risk adjustment tool to control for the effect of comorbidities. However, these two indexes indicated different directions of comorbidity influence: as the CDS comorbidity scores increases, patient medication adherence increases; however, as HRQL-CI mental aspect comorbidity score increases, adherence behavior decreases.

This may be due to the CDS and HRQL-CI mental aspect of index measured different underlying dimensions of comorbid burden. The CDS index, based on a list of medications representing 30 underlying disease conditions, [176, 177] attempts to provide a comprehensive picture of one's overall comorbid burden, while HRQL-CI mental aspect of index was originally developed to capture mental aspect of illness burden[376]. Since these two indexes might represent different underlying disease profiles, our results further demonstrated that mental illness burden could have a deterrent effect on medication adherence, while overall illness burden may enhance patients adhere to treatment. Consistently, previous research focused on diabetes patients also showed that mental aspect of illnesses, particularly depression, had negative impact on patient OAD medication adherence.[314, 315, 318] Also, research found that increasing overall illness burden was associated with higher medication adherence [60]. It is conceivable that patients with a higher number of chronic conditions could be better informed about diabetes and its complications and, therefore, would maintain greater rates of adherence despite their greater medication burden and numerous comorbidities. Or, increased perceived susceptibility and severity due to comorbid condition burden may motivate patients to improve their medication taking behavior.

Moreover, while analyzing healthcare utilization data in the context of hospitalization and emergency room visit, diagnosis-based indexes (e.g., the EI and CCI) had better predictive performance than medication-based index (e.g., the CDS), while for outpatient visits, the HRQL-CI mental aspect of index could be most valid comorbidity measure. These findings confirmed previous research findings, which

showed that diagnosis-based comorbidity scores had better validity in predicting healthcare utilization compared to medication-based index.[174]

To provide potential explanation for better predictive performance of HRQL-CI mental aspect comorbidity scores, we further conducted analyses to test the differences in mental illness and overall illness burdens between patients with high outpatient visits (defined as those having visits ≥90th percentile of visits among study population) and those with low outpatient visits (those having visits <90th percentile of visits). The results demonstrated that, although both overall illness and mental illness profiles between these two groups were statistically different, the magnitude of mental illness difference was larger than that of overall illness difference (t=-30.80, p<.0001 for the difference in mental illness scores measured by HRQL-CI mental aspect of index; t=-16.51, -29.22 and -26.40 for the differences in overall illness scores measured by CCI, EI and CDS, respectively). These results implied that mental illness burden between these two groups were more different than overall illness burden between them. This may lead to better predictive ability of the HRQL-CI mental aspect of comorbidity index than overall illness burden measurements, such as the EI.

Furthermore, for medical payment data, our findings supported previous research focused on Medicaid enrollees, which demonstrated that diagnostic measures (i.e., EI) had better predictive ability than pharmacy claims based risk assessment measures (i.e., CDS).[377] However, we were aware that this finding may be specific to the context of Medicaid setting because most previous literatures demonstrated that medication-based indexes had better predictive ability in healthcare expenditures than diagnosis-based comorbidity indexes [157, 350, 358, 375].

The present study findings should be interpreted in light of the following limitations. First, due to analyses based on claims data, the information on services not billed to the insurance system was not available (patients may receive treatment that is not submitted to their health plan for reimbursement and thus not included in claims-data). Second, correct categorization of insurance database information depends on correct coding by clinicians and other medical staff. The accuracy of

diagnostic coding can not be evaluated in a claims-based study. In coding each ICD-9-CM claims-based measurement, there exists the possibly that ruled out diagnoses that were assigned for billing purposes were misclassified as existing comorbidities.[76] Third, data on comorbidities were limited to conditions coded on medical claims within the time-frame studies. Fourth, caution should be used when generalizing results beyond the study population of continuously enrolled type 2 diabetes patients 18 to 64 years from Medicaid setting. Our sample was predominantly female and White. Additional studies should compare and validate these measures for health service use outcomes among other subpopulation or settings.

Lastly, although these comorbidity scores are useful because they are easy to use and they save time and resources, particularly in analyzing massive health care databases, they provided only limited information to manage comorbidities. All these comorbidity measures provide a summary score, which only can be used to study the impact of overall illness burden. However, understanding differential impacts of individual comorbidities could be more meaningful in terms of disease management and medical resource allocation. In fact, we found that mental illness as measured by the HRQL-CI mental aspect index had negative impact on medication adherence but overall illness as measured by the CDS had positive influence, which implied that differential influence of different types of comorbidities may exist. Understanding the direction and magnitude of individual comorbidities provide more informative knowledge to manage comorbidities. For example, more influential comorbidities could be targeted first or paid more attention. Further research could begin with identifying underlying dimensionality of comorbidities and then examining differential effects of different characteristics of comorbidity groups in health outcomes.

In conclusion, while more work is warranted to evaluate these findings can be supported in other population's theses results are, nevertheless, important for healthcare service researchers in the selection and use of existing alternative comorbidity indexes to assess and control for the effect of comorbidities on healthcare related outcomes. Also, since comorbidities have significant impact on

healthcare related outcomes in the Medicaid population with diabetes,[48, 49] a valid comorbidity measurement is important for healthcare providers to predict this population's health outcomes and for healthcare policy makers to identify patients at risk of high healthcare demand and spending due to their comorbid burden.

Table 16: Characteristics of Study Population (n=9,832)

Type	Variables	Mean (S.D.)	Frequency (%)
Predisposing (pre-index period)	**Age** (years) age≥50 age<50	44.81 (11.64) 56.18 (4.04) 37.30 (8.51)	-- 3,913 (39.80)
	Gender (female)	--	7,183 (73.06)
	Race	--	White:5,139 (52.27) Black:3,096 (31.49) Hispanic: 151 (1.54) Others: 1,239 (12.60) Multi-racial: 207 (2.11)
Need (pre-index period)	**Diabetes severity**	--	Nephropathy: 152 (1.55) Neuropathy: 506 (5.15) Retinopathy: 152 (1.55)
	Charlson Comorbidity index score (range: 0-35)	0.709 (1.27)	---
	Elixhauser index score (range: 0-30)	1.73 (1.55)	----
	Chronic Disease Scores (range: 0-18)	4.64 (2.96)	-----
	HRQL-CI scores Physical domain (range: 0-35) Mental domain (range: 0-25)	 4.15 (3.69) 3.65 (3.39)	------
Enabling (pre-index period)	**Type of health plan** Fee-for-service: Capitated plan: Both:	---	 5,448 (55.41) 3,203 (32.58) 1,181 (12.01)
	Type of provider: at least one endocrinologist visit (yes/no)	---	31 (0.32)
	Total no. of therapeutic classes	10.82 (10.82)	---
	Total no. of drugs supplied	557.35 (48.64)	---
Physicians' adherence to diabetes care (post-index period)	**at least 2 HbA1c tests/year**		6,950 (70.69)
	at least 1 LDL test/year		6,209 (63.15)
	at least 1 nephropathy screening/year		2,326 (23.66)

	at least 1 eye examination/year		4,297 (43.70)
	at least 1 foot examination/year		30 (0.31)
	Total physician treatment adherence score (range=0-5)	2.51 (1.11)	
Patient's adherence to diabetes medication (post-index period)	**Overall adherence (MPR)** for 3 selected OADs (Met, Sulfa, TZD) (n=9,832)	0.81 (0.26)	------
	MPR for mono-therapy (n=7,888) Met (n=62) Sulfa (n=5,949) TZD (n=1,877)	0.775 (0.23) 0.70 (0.21) 0.77 (0.24) 0.81 (0.21)	
	MPR for fixed dose regimens* (n=290)	0.783 (0.21)	
	MPR for switching or combination regimens (n=1,645)	0.95 (0.12)	
Healthcare utilization	**Total no. of hospital admission** Pre-index period: Post-index period:	 0.38 (0.09) 0.35 (0.096)	
	Total no. of emergency room visits Pre-index period: Post-index period:	 0.23 (0.09) 0.21 (0.74)	
	Total no. of outpatient visits Pre-index period: Post-index period:	 24.47 (14.85) 27.43 (17.45)	
Healthcare costs	**Total costs** Pre-index period: Post-index period:	 8,318.34 (24,051) 8,807.67 (27,204)	
	Diabetes care related costs Pre-index period Post-index period:	 1,282.93 (8,381) 2,257.99 (9,968)	

MPR: medication possession ratio, OAD: oral diabetic medication, Met: Metformin, Sulfa: Sulfonylurea, TZD: Thiazolidinediones

*4 fixed dose regimens of OAD available in the study period (2003-2007) are Glucovance™

(glyburide plus metformin), Avplusamet™ (rosiglitazone plus metformin), Metaglip™ (glipizide plus metformin), and Actaoplus Met™ (pioglitazone plus metformin)

Table 17: Spearman Rank Correlations of Comorbidity Indexes

	Charlson Comorbidity index	Elixhauser Index	HRQL-CI-physical aspect	HRQL-CI-mental aspect	Chronic Disease Score
Charlson Comorbidity index	1.000				
Elixhauser Index	**0.560**	1.000			
HRQL-CI-physical aspect	**0.545**	**0.654**	1.000		
HRQL-CI-mental aspect	0.390	**0.586**	**0.678**	1.000	
Chronic Disease Score	0.406	**0.588**	**0.600**	**0.521**	1.000

HRQL-CI: Health related Quality of Life Comorbidity Index
All correlations between any two different indexes were statistically significant (p<.0001)

Table 18: Predictive Validity of Comorbidity Indexes in Healthcare related Behaviors

Response variable: physician treatment adherence						
Predictor of interest	**Goodness of Fit for overall model**					**% change in EC[b]**
	LR[a]	**Deviance**	**McFadden's Adjusted-R^2**	**AIC**	**BIC**	
CCI	202.811	32031.175	0.14	32075.175	32233.414	-0.2, p=0.644
EI	210.958	32023.029	0.15	32067.029	32225.268	1.4, p=0.000
CDS	**219.710**	**32014.277**	**0.15**	**32058.277**	**32216.516**	**1.7, p=0.000**
HRQL-CI_physical	209.699	32024.287	0.15	32068.287	32226.526	0.6, p=0.00
HRQL-CI_mental	205.257	32028.730	0.14	32072.730	32230.969	0.4, p=0.015
Response variable: oral antidiabetic medication adherence						
Predictor of interest	**Goodness of Model Fit**					**% change in OR[c]**
	LR[a]	**Deviance**	**Max-rescaled R^2**	**AIC**	**BIC**	
CCI	495.941	12394.616	0.167	12430.616	12560.084	0.6, p=0.7596
EI	496.772	12393.785	0.167	12429.785	12559.253	1.7, p=0.3366
CDS	502.946	12387.611	0.168	12423.611	12553.079	**3.7, p=0.0078**
HRQL-CI_physical	496.2349	12394.322	0.167	12430.322	12559.791	-0.5, p=0.5335
HRQL-CI_mental	**506.1601**	**12384.397**	**0.168**	**12420.397**	12549.866	**-2.5, p=0.0013**

CCI: Charlson Comorbidity Index, EI: Elixhauser Index; CDS: Chronic Disease Score; HRQL-CI: Health related Quality of Life Comorbidity Index; EC: expected count; OR: odds ratio

a: X^2 test for the LR (likelihood ratio) for each individual model was statistically significant (p=0.000)

b: the analysis based on standard Poisson regression, the value reflects that, for every unit increase in comorbidity score, % change in expected count of physician treatment scores

c: the analysis based on logistic regression, the value reflects that, with one unit increase in comorbidity score, % change in the probability of being medication adherence

Table 19: Predictive Performance of Comorbidity Index in Healthcare Utilization

Predictor of interest	Goodness of Fit for overall model					% change in EC[b]
	LR[a]	Deviance	McFadden's Adjusted-R^2	AIC	BIC	
Response variable: number of hospitalization[a]						
CCI	**1122.286**	**13604.648**	**0.067**	**13706.648**	**14073.475**	**10.22, p=0.000**
EI	**1120.297**	**13606.636**	**0.067**	**13708.636**	**14075.463**	**10.23, p=0.000**
CDS	1110.060	13616.873	0.066	13718.873	14085.700	6.67, p=0.000
HRQL-CI_physical	1104.795	13622.138	0.066	13724.138	14090.965	3.21, p=0.000
HRQL-CI_mental	1111.111	13615.822	0.066	13717.822	14084.649	3.83, p=0.000
Response variable: number of emergency room visit[a]						
Predictor of interest	**Goodness of Model Fit**					**% change in EC[b]**
	LR[a]	**Deviance**	**McFadden's Adjusted-R^2**	**AIC**	**BIC**	
CCI	**1075.972**	**9394.461**	**0.090**	**9496.461**	**9863.288**	**9.2, p=0.000**
EI	**1074.866**	**9395.567**	**0.090**	**9497.567**	**9864.394**	**9.5, p=0.000**
CDS	1072.649	9397.784	0.090	9499.784	9866.611	7.4, p= 0.000
HRQL-CI_physical	1067.265	9421.121	0.089	9505.168	9871.995	3.2, p=0.002
HRQL-CI_mental	1072.028	9398.406	0.090	9500.406	9867.232	4.0, p= 0.000
Response variable: number of outpatient visit						
Predictor of interest	**Goodness of Model Fit**					**% change in EC[b]**
	LR[a]	**Deviance**	**McFadden's Adjusted-R^2**	**AIC**	**BIC**	
CCI	8117.506	76861.945	0.094	76961.945	77321.579	6.6, p=0.000
EI	8298.863	76680.588	0.096	76780.588	77140.222	9.8, p=0.000
CDS	8131.509	76847.942	0.094	76935.942	77252.420	5.2, p= 0.000
HRQL-CI_physical	8245.286	76734.165	0.095	76836.165	77202.992	3.9, p=0.000
HRQL-CI_mental	**8438.714**	**76540.737**	**0.098**	**76640.737**	**77000.371**	5.3, p= 0.000

CCI: Charlson Comorbidity Index, EI: Elixhauser Index; CDS: Chronic Disease Score; HRQL-CI: Health related Quality of Life Comorbidity Index; EC: expected count
a: X^2 test for the LR (likelihood ratio) for each individual model was statistically significant (p=0.000)
b: the analysis based on zero-inflated negative binomial regression, the value reflects that, every unit increase in comorbidity score, % change in expected count of healthcare utilization (e.g., the number of hospitalization)

Table 20: Predictive Performance of Comorbidity Index in Healthcare Expenditures

Response variable: total medical costs[a]						
Predictor of interest	**Goodness of Fit for overall model**					**% change in Exp(b)[b]**
	LR[a]	**Deviance**	**Pseudo-R^2**	**AIC**	**BIC**	
CCI	5382.44	18567.377	0.272	19.626	-71474.98	11.51, p=0.000
EI	**5509.74**	**18452.979**	**0.278**	**19.613**	**-71589.37**	**15.32, p=0.000**
CDS	5374.54	18576.069	0.271	19.626	-71466.28	8.37, p= 0.000
HRQLCI_ physical	5391.14	18562.687	0.272	19.625	-71479.67	4.99, p=0.000
HRQL-CI_mental	5498.35	18460.485	0.277	19.614	-71581.87	6.48, p= 0.000
Response variable: diabetes care related costs[a]						
Predictor of interest	**Goodness of Model Fit**					**% change in Exp(b)[b]**
	LR[a]	**Deviance**	**Pseudo-R^2**	**AIC**	**BIC**	
CCI	5515.87	27111.634	0.322	16.890	-62939.91	14.93, p=0.000
EI	**6235.12**	**26661.728**	**0.364**	**16.817**	**-63389.82**	**28.67, p=0.000**
CDS	5808.91	26924.468	0.339	16.860	-63127.08	16.12, p= 0.000
HRQL-CI_ physical	5989.68	26829.871	0.349	16.842	-63221.68	9.89, p=0.000
HRQL-CI_mental	5824.17	26879.122	0.340	16.858	-63172.42	8.55, p= 0.000

CCI: Charlson Comorbidity Index, EI: Elixhauser Index; CDS: Chronic Disease Score; HRQL-CI: Health related Quality of Life Comorbidity Index; Exp(b): exponentiated log-transformed value of the parameter estimate

a: X^2 test for the LR (likelihood ratio) for each individual model was statistically significant (p=0.000)

b: the analysis based on the Generalized linear model with gamma family and log link, the value reflects that, every one unit increase in comorbidity score, % change in expected medical expenditures

Chapter

5. Dissertation Manuscript 2: Title: Assessment of Discriminative Validty of Comorbidity Indexes in Health related Behaviors and Outcomes in Medicaid Enrollees with Type-2 Diabetes

Abstract:

Background: The predictive validity of the Charlson Comorbidity Index (CCI), Elixhauser Index (EI), Chronic Disease Score (CDS), and Health related Quality of Life Comorbidity Index (HRQL-CI) has been examined individually, few direct comparison research in discriminative performance among these alternative indexes in Medicaid diabetes patients.

Objective: To assess and compare existing alternative comorbidity indexes in discriminating patients varying in demographics, healthcare related behaviors (physician treatment adherence and patient medication adherence), healthcare utilization (hospitalization, emergency room and outpatient visits) and expenditures characteristics.

Methods: Using the MarketScan™ Medicaid database from 2003 to 2007, type 2 diabetes patients were targeted. Discriminative validity of comorbidity index was assessed using the c statistic, which represents the area under the Receiver Operator Characteristic curve. The C-statistic is a measure of a model's ability to discriminate between those subjects who experience the outcome of interest vs. those who do not, with values ranging from 0.5 (no discrimination beyond chance) to 1.0 (perfect discrimination). The SAS software version 9.2 was used for data management and analysis.

Results: 9,832 patients were included, with mean age of approximate 45 years and majority of population was female (73%) and White (52%). The CDS had best

performance in discriminating age subgroups (c=0.61) and patients with being medication adherent or not (c= 0.56). The CDS and HRQL-CI physical and mental aspects of index performed similarly in discrimination in physician treatment adherence (c=0.60 for both indexes). The EI had best discriminative performance in healthcare utilization and costs, while the HRQL-CI physical aspects of index performed similarly to the EI in the context of hospitalization admission (c=0.62 for both) and the HRQL-CI mental aspects of index performed similarly to the EI in outpatient visits (c=0.74 for both).

Conclusion: The CDS could be most appropriate measure to differentiate patients varying in demographic characteristics, physician treatment and medication behaviors, while the EI could serve as the first choice of comorbidity measure to identify patients at high risk of being medical resource demand and economic burden. The HRQL-CI could serve as alternative measure to EI in discrimination of healthcare utilization in the context of hospitalization and outpatient visits.

Introduction

The term "comorbidity" refers to any distinct additional entity that has existed or may occur during the clinical course of a patient who has the index disease under study.[7] With technological advances and improvements in medical care and policy, an increasing number of patients survive medical conditions that used to be fatal. Because of this phenomenon, and parallel to the aging of the population, a growing proportion of patients present with multiple coexisting medical conditions. It has been shown that 57 million Americans had multiple chronic conditions in 2000 and that this number will rise to 81 million by 2020 [1], with a consistent trend worldwide [2-6]. Researches have shown that comorbidities had a significant impact on many facets of healthcare outcomes, including mortality [37, 38, 358, 372-374], healthcare utilization [174, 358, 374] and costs [157, 358, 375].

Measurement of comorbidity is particularly important in epidemiological and health services research. For controlling for confounding in epidemiologic analyses in which claims based data are used, comorbidity scores are useful tools. However, little is known about the relative performance of various available comorbidity indexes in predicting a variety of healthcare outcomes [32]. Particularly measures often seem to be chosen for convenience rather than performance. The construct "comorbidity" reflects the aggregate effect of all clinical conditions a patient might have, excluding the disease of primary interest[378]. Because there is no gold standard for assessing comorbidity, investigators should validate alternative measures by determining their ability to predict critical health outcomes, such as mortality, healthcare utilization and costs.[33] Because the predictive performance of alternative comorbidity measures depends in part on the outcome of interest, investigators should choose comorbidity index specific to their study population and outcome of interest.[187, 188]

Although many alternative approaches to assessing comorbidity using administrative data have been validated, three common indices are the Charlson Comorbidity Index (CCI) [17], Elixhauser Index (EI) [33], and the Chronic Disease

Score (CDS) [35]. The Charlson Comorbidity Index (CCI), a disease severity weighted index of comorbidity, is perhaps best studied, validated, and widely used. The weightings in the CCI were first developed using chart review data collected from an index hospitalization to predict 1-year survival and validated on an independent population of breast cancer patients. Subsequently, numerous researchers have adapted the CCI for use with administrative data that use the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM). The CCI has been shown to predict mortality [154, 155] and hospitalization outcomes in a variety of patient populations [20, 156, 157]. The EI also uses ICD-9-CM codes to identify 30 categories of comorbid illness. Previous research has shown that the EI outperformed to the CCI in predicting mortality [37, 38]. The CDS is a pharmacy-claims based index and has been demonstrated better predictive ability in healthcare expenditures, compared to diagnosis-based indexes.[32, 39] The CCI scores are the weighted based scores, which is the sum of the weights for each comorbid condition a patient had, while the EI or CDS scores are the sum of conditions a patient had without any weighting approaches.

The Health related Quality of Life Comorbidity Index (HRQL-CI) is a newer diagnosis-derived measure that is predictive of HRQL as measured by the SF-12 PCS (physical component summary score) and MCS (mental component summary score) using the Medical Expenditure Panel Survey (MEPS) database. It also has weighting scheme to account for differential severity of comorbid conditions. It has been shown to outperform to the CCI in predicting the HRQL in general population and asthma subsample.[41] Further research need to compare its predictive performance with other existing measures (e.g., EI and CDS) and in other context of health outcomes.

Medicaid population is vulnerable population often affected by multiple medical conditions and therefore, additional chronic illnesses are common in these patient groups.[42] Among different diseases, the prevalence of diabetes in Medicaid patients was twice than in the general population (8% in Medicaid versus 4% in general population).[42] In fact, diabetes disease essentially places patients at high risk of heart disease, blindness, kidney failure, extremity amputations, and

other medical or comorbid conditions [50, 51]. Most adults with diabetes have at least one comorbid chronic disease [52] and as many as 40% have 3 or more [6, 53]. Thus, Medicaid diabetic beneficiaries are unique in terms of comorbidity research.

To date, discriminative validity of the CCI, EI, CDS and HRQL-CI indexes has not been well documented and compared. The CCI and EI were developed on the basis of predicting mortality and/or hospitalization-related outcomes and the HRQL-CI was primarily attempted for predicting the HRQL outcome data, but their ability to differentiate patients with different demographic characteristics (i.e., age) or with different healthcare related behaviors, such as medication adherence, has not been studied yet. The importance of assessing the discriminative ability of comorbidity measure is that comorbidity index function not only as risk adjustment tool for outcome research but also as risk identifier to differentiate people varying in the level of medical need because of their illness burden. Also, understanding the discriminative validity of comorbidity measures could assist medical resource allocation in which comorbidity measure differentiates patients with high and low medical consumption due to their illness burden.

The present study was aimed to assess discriminative validity of existing alternative comorbidity indexes in three aspects of endpoints: demographics, healthcare related behaviors and outcomes, and then to compare the discriminative ability of the CCI with other indexes to demonstrate discrimination improvement of comorbidity scores based on these latter developed indexes (EI, CDS and HRQL-CI).

Methods

Data source

This retrospective, observational, cohort study used the data from Thomson's MarketScan™ Medicaid dataset[355] from 2003 to 2007. The MarketScan™ Medicaid dataset is a widely used source of data for many studies in different disease areas. It represents eight states of varying sizes across the United States. The database includes healthcare coverage eligibility and service use of individuals enrolled in state Medicaid programs from eight states. It includes

outpatient and inpatient services, prescription drug claims, long-term care, and enrollment data. In addition to standard demographic variables such as age and gender, the database also includes variables such as ethnicity, Medicare eligibility, and his or her provider's specialty.

We further classified the study period into three specific intervals: (1) index drug identification period was the time window from 2004 to 2006. Within 24 months, the date when a patient's first OAD prescription claim occurred was defined as index date and the drug of the first OAD prescription is defined as index prescription. (2) Pre-index period was 12 months prior to the index date (starting from a patient's index date and look-back in time up to 12 months) and was used to verify continuous Medicaid eligibility as well as to identify baseline characteristics before starting any therapies. This also helped determine patients who did not have any OAD claims in this period and confirm a new start of the OAD medications in the index date. (3) Post-index period was12months after the index date (starting from a patient's index date and look-forward in time up to 12 months) and was used to ensure that patients had at least 12 months of follow-up period. Healthcare related behaviors (e.g., medication taking behavior) and outcomes (e.g., costs) were examined in this period

Sample selection criteria

In the MarketScan™ database, individuals who satisfied all six following criteria were included in study cohort. (1) At least one outpatient or inpatient diagnosis of type 2 diabetes diagnosis based on the ICD-9-CM=250.0x-250.9x, where x=0 or 2. (2) Aged 18 to 64 years old at the index date. The reason for excluding individuals aged 65 years and above was that these people may be dual beneficiaries (Medicare and Medicaid enrollees) and therefore obtaining complete data on these patients may not be available. (3) Continuous enrollment in Medicaid in the pre- and post-index periods. The continuous enrollment criterion ensures that all study subjects had the same follow-up period, and therefore reduces bias due to failure to follow-up. (4) At least one filled prescription for OAD. (5) Drug naïve patients in pre-index period and newly starting OAD medication therapy during the index period window (2004-2006). Considering that newly treated patients

beginning their first course of medication are likely to have different medication use behaviors and responses to medication than are those already on a particular therapy, only newly started cases were included to understand the medication use behavior based on individuals who are naïve to OADs. (6) Patients with continuous medication therapy was defined by 2 following criteria: (a) Therapy without a lapse of> 60 days between date of days' supply expiration of any prescription fill and the subsequent claim date (days between end date of first fill and date of next fill), and (b) At least 2 prescription on the index medication.

Study variables

The selection of study variables were based on the literatures, Aday-Andersen Model for healthcare utilization [64] and clinical expertise. We chose four types of endpoints: demographics, healthcare related behaviors, healthcare related utilization and expenditures. We hypothesized that comorbidity measure can discriminate patients varying in each of these endpoints. The rationale to study discriminative ability of comorbidity measure in demographics is that the elderly experienced more comorbidity burden than the younger.[6, 379] Illness burden could be different between elderly and young patients. Also, in diabetes patients, racial minorities such as African American, Latinos and Native Americans, had higher illness burden and mortality than white Americans.[286, 365, 366, 380] Therefore, we assume that comorbidity scores are able to differentiate patients varying in the age and racial demographic characteristics.

Moreover, we utilized the Aday-Andersen Model to explain determinants of healthcare utilization[64]. This model demonstrates healthcare-seeking behaviors, such as the use of medication, by classifying determinants of healthcare utilization into predisposing, enabling, and need-related factors. Need related factors can be defined as an individual's health status as he/she perceives it and/or as evaluated by a healthcare provider and measured by examining the level of illness or presence of comorbidities. It is assumed that one's comorbidities are associated with the healthcare related behaviors and related to healthcare utilization and costs. In this regard, we hypothesized that one's comorbidities were associated with healthcare related behaviors, utilization and costs, and comorbidity scores can be used to

differentiate patients varying in these healthcare outcomes. The following described each of study variables.

First, four types of study endpoints were selected: demographics, including age and race; healthcare related behaviors, including physician treatment adherence and patient medication adherence; healthcare related utilization, including hospitalization, emergency room (ER) visits and outpatient visits; and expenditures, including total medical and diabetes care related costs. Healthcare related behaviors, utilization and expenditures were measured in post-index period.

Patient's age was defined as year at the start of the first OAD therapy (index date) minus the year of birth. Patient's race/ethnicity was also treated as a dummy variable, where White=0, Non-White=0 (including the Black, Hispanics, and Others as defined in the MarketScan™ data).

Physician's treatment compliance score was based on five recommended examinations by the American Diabetes Association (2005) [204], including at least two hemoglobin tests (HbA1c) per year, a cholesterol test per year, an eye examination per year, a mircoalbuminuria test per year and a foot examination per year. The final score was calculated as the sum of the number of recommended procedures completed. A person receiving more than 2 HbA1c tests was only given credit for it once. Except for the HbA1c test, a person having the same examination multiple times in the allotted time (e.g., more than one cholesterol screening within one year) was only given credit for it once. Treatment adherence scores range from zero (no recommended procedures performed) to five (all recommended procedures provided).

Medication adherence in this study was defined as patient's adherence to a new start of OAD, particularly focused on 3 common OAD as index drugs, including sulfonylureas, metformin, and thiazolidinediones and their fixed-dose regimens, which were available in our study period, including Glucovance™ (glyburide plus metformin), Avplusamet™ (rosiglitazone plus metformin), Metaglip™ (glipizide plus metformin), and Actaoplus Met™ (pioglitazone plus metformin). Prescription refill patterns were used as a measure of medication adherence under the assumption that a prescription filled was a prescription taken. Medication

possession ratio (MPR) was used to measure adherence. The observation period begins with the first date of dispensing (index date) and ends as the dispensing date of the last prescription within post-index period. Information on all filled prescriptions was extracted from the pharmacy claims file in MarketScan™ Medicaid data. The formulations for computing the MPR were as follows. For monotherapy or fixed-dose regimen: MPR=total day's supply obtained/(date of the last claim—date of the first claim+day's supply of the last claim); for combination therapy (e.g., using more than one types of index drug or switching drugs): MPR=total day's supply obtained/n*(date of the last claim—date of the first claim+day's supply of the last claim) (n=no. of OAD combined, e.g., for dual therapy, n=2).

Four alternative comorbidity index scores were constructed: Charlson Comorbidity index (CCI)[20], Elixhauser index (EI)[33], Chronic Disease Score (CDS)[176], and Health related Quality of Life Comorbidity index (HRQL-CI)[41]. Scores derived from the CCI, EI, and HRQL-CI indexes were based on a list of the selected ICD-9-CM diagnosis codes derived from inpatient, emergency room and outpatient medical claims, while the CDS was estimated utilizing the selected NDC numbers on outpatient prescription drug claims to determine prescribed drug usage. We excluded the diagnostic codes of type 2 diabetes because of the disease population studied. Comorbidity scores were all estimated in pre-index period.

Statistical analysis

The descriptive statistics of population characteristics were performed, including means, standard deviation, frequency and proportion, are performed for all study variables. The correlations between comorbidity indexes were assessed using Spearman rank correlations.

The *c*-statistic was employed to quantify discriminative ability of each individual comorbidity index. For binary outcomes, the *c*-statistic is identical to the area under the receiver operating characteristic curve (ROC curve). The ROC curve is a plot of true-positive rate (e.g. percentage of patients having the outcome and correctly classified as diseased, or sensitivity) versus false-positive rate (e.g.

percentage of patients having the outcome and incorrectly classified as diseased, or 1-specificity) evaluated at consecutive threshold values of the predicted probability.

The area under the ROC curve represents the probability that a patient with the outcome has a higher predicted probability than a patient without the outcome for a random pair of patients consisting of one patient with and one patient without the outcome. In the other words, c statistics measures discrimination, that is, the ability of the measure to correctly classify those with and without the event of interest. Values of c statistic range from 0 to 1. A useless discriminative ability of the measure, such as a coin flip, would realize an area of 0.5 (the measure has effectively 50% sensitivity and 50% specificity). When the area is 1, the measure discriminates perfectly (the measure achieves both 100% sensitivity and 100% specificity). The large the area, the better the measure.[361] Since there is no golden rule for classifying the accuracy of discriminative ability of a measure based on the c statistics value, we applied a common guide: c statistics values between 0.5- 0.75 as fair, 0.75-0.92 as good, 0.92-0.97 as very good, and 0.97-0.1 as excellent discriminative ability.[381]

In the present study, the extent to which a comorbidity index can accurately differentiate six types of dichotomized subgroups, including: (1) 2 age subgroups based on a age cutoff of 50 years: Older (50-64 years) versus Younger (18-49 years), (2) 2 racial subgroups: White versus non-White (including Black, Hispanic and Others as defined in the MarketScan™ dataset), (3) 2 groups classified using a cutoff of physician treatment adherence score of 4: Better treatment (score≥4) versus Poor treatment (score<4), (4) 2 groups classified using a cutoff of the MPR value of 0.8: medication adherent (MPR≥0.8) versus non-adherent (MPR<0.8) (5) subgroups varying in healthcare related utilization: Higher users (visits≥ 90th percentile of visits among study population) versus Lower users (visits< 90th percentile), (6) subgroups varying in healthcare expenditures: High spending (costs ≥ 90th percentile of costs among study population) versus Low spending (costs< 90th percentile).

To compare discriminating abilities of comorbidity indexes, Delong et al's (1988) methods for correlated ROC curves comparison[362] were applied using the

ROC and ROCCONTRAST statements in PROC LOGIST procedure in SAS software version 9.2[363]. We chose the CCI as the reference index for the purpose of two indexes comparison because it is most widely used comorbidity measure. Data files were identified and available to the researcher in SAS format. Data management and analysis was conducted using SAS software version 9.2.[363]

Results

Characteristics of study population

The descriptive results for the 9,832 individuals who comprised our study cohort are as summarized in table 21. Study population were on average age of 44.81 (±11.64) years old, with 39.8% of population who were aged 50 years or above, and majority of population was female (73%), White (52%). Mean scores ranged from 0.709 (±1.27) for the CCI, 1.73 (±1.55) for the EI, 4.64 (±2.96) for the CDS, and 4.15 (±3.69) and 3.65 (±3.39) for HRQL-CI physical and mental aspects of indexes, respectively.

Mean physician treatment adherence score was 2.51(±1.11), with 19.63% of population whose scores were≥4. Average MPR was 0.80 (±0.22), with 63.31% of population whose MPR was ≥0.8.

Regarding healthcare utilization, average numbers of ER visits, non-ER hospitalization and outpatient visits in post-index period were 0.21 (±0.74), 0.35 (±0.096) and 27.43 (±17.45), respectively. For people who consumed healthcare utilization at or above 90th percentile of total use among study population, average numbers of ER visits, non-ER hospitalization and outpatient visits were 1.60 (±1.40), 1.65 (±1.46) and 109.08 (±71.14), respectively.

For medical expenditures, average total medical costs and diabetes care related costs per person in post-index period were 8,807.67 (±27,204) and 2,257.99 (±9,968), respectively. For individuals who spent at or above 90th percentile among study population, average total medical costs and diabetes care related costs per person in post-index period were 18,986.80 (±26,078.41) and 397.55 (±529.03), respectively.

Correlations of Comorbidity Indexes

The strength of the correlations between the different indexes varying across types of measurements was given in table 22. The correlations between any two of the ICD-9-CM claims-based indexes (the CCI, EI and HRQL-CI physical and mental aspects of indexes) were fair (ρ>0.5), with one exception of small correlation between the CCI and HRQL-CI mental aspect of index (ρ=0.39). In addition, there were fair correlations between any one of the ICD-9-CM claims-based indexes and the pharmacy claims-based index (the CDS), with one exception of slightly low correlation between the CCI and CDS (ρ=0.41).

Discriminative validity of Comorbidity Indexes

As summarized in table 23, first, to differentiate demographic subgroups (older versus younger and White versus non-White), all comorbidity index models had fair discriminative ability (all *c* values between 0.5 and 0.75), with the CDS's as the best (0.6081 and 0.6017 for discrimination for age and racial subgroups, respectively).

When using the CCI as a reference in age subgroups discrimination, the discriminative validity of CDS was statistically better (c value difference (Δ*c*): 0.0180 (±0.00614), p=0.0033), while HRQL-CI mental aspect of index had inferior discriminative ability to the CCI (Δ*c*= -0.0690(±0.00923), p<0.001). For racial subgroups discrimination, compared to the CCI, all other comorbidity indexes each demonstrated better discriminative ability. (Δ*c*=0.0223 (±0.00505), 0.0859 (±0.00585), 0.0620(±0.00517) and 0.0805 (±0.00591) for the contrast between the CCI and EI, CDS, HRQL-CI physical and mental aspect of indexes, respectively; all p value<0.0001) (Graphically displayed in figure 14)

To discriminate patients varying in healthcare related behaviors, all indexes demonstrated fair discriminative ability, with the CDS having the best performance. When comparing with the CCI, the CDS showed significantly better discrimination in physician treatment adherence (Δ*c*=0.0223 (±0.00505), p=-.0115). To discriminate patients with and without adherence to OAD medication, the CDS, EI and HRQL-CI physical aspect of index all outperformed to the CCI, while the HRQL-CI mental aspect of index was inferior to the CCI (Δ*c*=0.0186 (±0.00517) p=0.0003, Δ*c*=0.0405

(±0.00607) p<0.0001, Δ*c*=-0.0158(±0.00619) p=0.0108, for the contrast between the CCI and EI, between the CCI and CDS and between the CCI and HRQL-CI mental aspect of index, respectively). (Graphically displayed in figure 15)

Regarding discrimination in healthcare utilization, across different types of healthcare resource use (non-ER hospitalization, ER visits and outpatient visits), the EI demonstrated the best discriminative ability (*c*=0.65, 0.62 and 0.74 for discrimination for ER visits, Non-ER hospitalization and outpatient visits, respectively). While the HRQL-CI physical aspect of index had similar discriminative performance in non-ER hospitalization (*c*=0.62) with the EI and HRQL-CI mental aspect of index demonstrated similar discriminative performance in outpatient visits with the EI (*c*=0.74). As compared to the CCI, only EI had statistically better than the CCI in the discrimination of ER visits (Δ*c*=-0.0236(±0.0074) p=0.0014), the EI and HRQL-CI physical aspect of index both outperformed to the CCI in discriminating patients with high and low non-ER hospitalization (Δ*c*=0.0148 (±0.0061) p=0.0158, Δ*c*=0.0155 (±0.0063) p=0.0133, for the contrast between the CCI and EI and between the CCI and HRQL-CI physical aspect of index, respectively), and all other indices were superior to the CCI in discriminating patients with high and low outpatient visits (Δ*c*=0.1155 (±0.0084), 0.0974 (±0.0094), 0.0767(±0.0087) and 0.1172 (±0.0101) for the contrast between the CCI and EI, CDS, HRQL-CI physical and mental aspect of indexes, respectively; all p value<0.0001). (Graphically displayed in figure 16)

Moreover, to identify patients as being high medical cost burden (as defined by medical spending at or above 90th percentile among study population), all comorbidity indexes showed fair discriminative ability (all *c* values close to 0.6). Among the indexes, the EI demonstrated the best performance in both total and diabetes care specific medical costs (*c*=0.6959 and 0.6468, for total and diabetes care related costs, respectively). As compared to the CCI, the EI and HRQL-CI physical aspect of index both showed the better discriminative performance. (discrimination for total costs: Δ*c*=0.0572 (±0.00827) p<0.0001 and 0.0251 (±0.00862) p=0.0036, for the contrast between the CCI and EI and between the CCI and HRQL-CI physical aspect of index, respectively; discrimination for diabetes care

related costs: Δ*c*=0.0348 (±0.0087) p<0.0001 and 0.0328 (±0.00888) p=0.0002, for the contrast between the CCI and EI and between the CCI and HRQL-CI physical aspect of index, respectively) (graphically displayed in figure 17).

Discussion

The present study contributed to research by enhancing the knowledge regard to comparative discriminative validity of existing alternative comorbidity measures across a spectrum of important endpoints, including demographics, healthcare care related behaviors and outcomes, and in the context of Medicaid diabetic population. The following four points discuss our main research findings.

First, to differentiate people based on their demographics, the CDS provided the best discriminative ability among alternative measures. To our knowledge, this was the first study to assess discriminative validity of comorbidity measures in patients varying in the demographic characteristics. One potential implication is that the comorbidity index may not only function as risk adjustment tool but also be used as a risk identifier to identify particular disadvantaged demographic populations who are in need for medical attention due to their illness burden, such as the elderly and racial minorities. To identify these disadvantaged demographic populations is critical in the context of Medicaid setting. In fact, the vast majority of diabetes in Medicaid are elderly, who are already an expensive population that typically has multiple comorbidities, and they spend on average about three times more than adults or children with diabetes.[48] Also, issues of racial disparities have been identified in the Medicaid setting [382-385]. Research has shown that people with diabetes in racial minority groups had lower access to medical care due to factors such as a higher rate of no health insurance and living in areas with fewer primary care physicians, which attribute to racial disparity ratios for diabetes death rates [386]. African Americans, Latinos and Native Americans experience a 50-100% higher burden of illness and mortality as a result of diabetes than white Americans. These racial subgroups had worse glycemic control than other groups. So, comorbidity index, particularly the CDS, could be used to identify these

disadvantaged demographic groups and then appropriate interventions for improving quality of care can be delivered to people in need properly.

Second, the CDS also demonstrated the best validity in discriminating patients varying in healthcare related behaviors, including physician treatment pattern and medication taking behavior. No research has particularly focused on discriminative validity of comorbidity measures in healthcare related behaviors; however, this assessment is important in Medicaid setting when many states have gradually shifted their focus to disease management programs with a specific emphasis on diabetes. Health provider prescribing and patient medication taking behaviors are two important perspectives in disease management and are most considered in the area of diabetes disease management. Therefore, based on our findings, we suggested that the CDS could be used as a tailoring indicator for behavioral interventions to healthcare providers and patients.

For example, patients having multiple conditions may create considerable management complexity, forcing clinicians to consider and prioritize a large array of recommended care, possibly replacing valuable time in the office visit that could be spent addressing issues which have a greater impact on patient health outcomes, therefore, physicians may have a difficulty to adherent disease-specific treatment guidelines, such as diabetes guideline, when treating patients with multiple comorbid conditions[226, 271] In this regard, based on the CDS comorbidity scores, the physicians who have patients with higher illness burden could be identified and then interventions for improving their quality of care, such as education about appropriate treatment for patients with multiple illnesses, could be delivered to them. Similarly, based on the CDS comorbidity scores, patients with poor medication adherence could be differentiated so behavioral program for improving their medication adherence could be provided to them.

Third, overall, the EI demonstrated the best discriminative validity in healthcare utilization, which supported previous research finding that diagnosis-based comorbidity indexes outperformed medication-based measures in risk adjustment for healthcare utilization.[174] In addition, our results also showed that the HRQL-CI physical aspect of index could serve as an alternative measure to the EI

in discrimination of non-ER visits, while the HRQL-CI mental aspect of index could be an alternative measure to the EI in discriminating outpatient visits.

Fourth, for healthcare cost discrimination, the EI also demonstrated the best performance, a consistent result with previous research in Medicaid setting.[377] However, we were aware that this finding may be specific to the context of Medicaid setting because most previous literatures demonstrated that medication-based indexes had better predictive ability in healthcare expenditures than diagnosis-based comorbidity indexes [157, 350, 358, 375].

Finally, the present study had some limitations, which should be cautious in the interpretation of our research findings. First, due to analyses based on claims data, the information on services not billed to the insurance system was not available (patients may receive treatment that is not submitted to their health plan for reimbursement and thus not included in claim data). Second, correct categorization of insurance database information depends on correct codlings by clinicians and other medical staff. The accuracy of diagnostic coding can not be evaluated in a claims-based study. Also, in coding each ICD-9-CM claims-based measurement, there exists the possibly that ruled out diagnoses that were assigned for billing purposes were misclassified as existing comorbidities.[76]
Third, data on comorbidities were limited to conditions coded on medical claims within the time frame studies. Fourth, caution should be used when generalizing results beyond the study population of continuously enrolled type 2 diabetes patients 18 to 64 years from Medicaid setting. In addition, our sample was predominantly female. Additional studies should compare and validate these measures for health service use outcomes among other patient populations**.**

In conclusion, Medicaid enrollees with diabetes are a high-cost population with significant health complications and high levels of healthcare use. An effective strategy to identify patients at risk of poor disease management or health outcomes is the first step in designing intervention for improving their quality of care and health outcomes, and to reduce medical spending. Our research findings suggested potential risk identifiers to differentiate disadvantaged populations characterized by their demographic, healthcare related behaviors, utilization and spending.

Identifying these disadvantaged populations is important to improve their quality of care and healthcare outcomes and to allocate medical resources for people in need appropriately, particularly among the Medicaid beneficiaries with diabetes, a population who tends to be older or disable with severe health complications, high healthcare demand and spending due to their illness burden.

Table 21: Characteristics of Study Population (n=9,832)

Type	Variables	Mean (S.D.)	Frequency (percent %)
Predisposing (pre-index period)	**Age** (years) age≥50 age<50	44.81 (11.64) 56.18 (4.04) 37.30 (8.51)	-- 3,913 (39.80)
	Gender (female)	--	7,183 (73.06)
	Race	--	White:5,139 (52.27) Black:3,096 (31.49) Hispanic: 151 (1.54) Others: 1,239 (12.60) Multi-racial: 207 (2.11)
Need (pre-index period)	**Diabetes severity**	--	Nephropathy: 152 (1.55) Neuropathy: 506 (5.15) Retinopathy: 152 (1.55)
	Charlson Comorbidity index score (range: 0-35)	0.709 (1.27)	---
	Elixhauser index score (range: 0-30)	1.73 (1.55)	----
	Chronic Disease Scores (range: 0-18)	4.64 (2.96)	-----
	HRQL-CI scores Physical domain (range: 0-35) Mental domain (range: 0-25)	 4.15 (3.69) 3.65 (3.39)	------
Enabling (pre-index period)	**Type of health plan** Fee-for-service: Capitated plan: Both:	---	 5,448 (55.41) 3,203 (32.58) 1,181 (12.01)
	Type of provider: at least one endocrinologist visit (yes/no)	---	31 (0.32)
	Total no. of therapeutic classes	10.82 (10.82)	---
	Total no. of drugs supplied	557.35 (48.64)	---
Physicians' adherence to diabetes care (post-index	**at least 2 HbA1c tests/year**		6,950 (70.69)
	at least 1 LDL test/year		6,209 (63.15)

period)	**at least 1 nephropathy screening/year**		2,326 (23.66)
	at least 1 eye examination/year		4,297 (43.70)
	at least 1 foot examination/year		30 (0.31)
	Total physician treatment adherence score (range=0-5)	2.51 (1.11)	
Patient's adherence to diabetes medication (post-index period)	**Overall adherence (MPR)** for 3 selected OADs (Met, Sulfa, TZD) (n=9,832)	0.81 (0.26)	------
	MPR for mono-therapy (n=7,888) Met (n=62) Sulfa (n=5,949) TZD (n=1,877)	0.775 (0.23) 0.70 (0.21) 0.77 (0.24) 0.81 (0.21)	
	MPR for fixed dose regimens* (n=290)	0.783 (0.21)	
	MPR for switching or combination regimens (n=1,645)	0.95 (0.12)	
Healthcare utilization	**Total no. of hospital admission** Pre-index period: Post-index period:	 0.38 (0.09) 0.35 (0.096)	
	Total no. of emergency room visits Pre-index period: Post-index period:	 0.23 (0.09) 0.21 (0.74)	
	Total no. of outpatient visits Pre-index period: Post-index period:	 24.47 (14.85) 27.43 (17.45)	

Healthcare costs	**Total costs** Pre-index period: Post-index period:	 8,318.34 (24,051) 8,807.67 (27,204)	
	Diabetes care related costs Pre-index period Post-index period:	 1,282.93 (8,381) 2,257.99 (9,968)	

MPR: medication possession ratio, OAD: oral diabetic medication, ER: emergency room
*All cutoffs on 90th percentile of visits (or costs) among study population

Table 22: Spearman Rank Correlations of Comorbidity Indexes

	Charlson Comorbidity index	Elixhauser Index	HRQL-CI-physical aspect	HRQL-CI-mental aspect	Chronic Disease Score
Charlson Comorbidity index	1.000				
Elixhauser Index	**0.560**	1.000			
HRQL-CI-physical aspect	**0.545**	**0.654**	1.000		
HRQL-CI-mental aspect	0.390	**0.586**	**0.678**	1.000	
Chronic Disease Score	0.406	**0.588**	**0.600**	**0.521**	1.000

HRQL-CI: Health related Quality of Life-Comorbidity Index

All correlations between any two different indexes were statistically significant ($p<.0001$)

Table 23: Area under the Receiver Operating Characteristic Curve for Comorbidity Index's Ability in Discriminating Demographic Subgroups, Medication Adherence Behavior, and Healthcare Expenditures

Outcome variable*	**Predictor**	**Each Comorbidity Index**		**Contrast between the Indexes** (the CCI as a reference)	
		c ****	**95% CIs**	**Δc** (SE.)	**Chi-square** (p value)
Age:	CCI	0.59	0.58, 0.60	---	---
Younger vs.	EI	0.60	0.58, 0.61	0.0056(0.0052)	1.1434 (0.2849)
Older	**CDS**	**0.61**	**0.60, 0.62**	0.0180 (0.0061)	8.6335 (0.0033)
	HRQL-CI_physical	0.59	0.58, 0.61	0.0045(0.0054)	0.6898 (0.4062)
	HRQL-CI_mental	0.52	0.51, 0.53	-0.0690(0.0092)	55.8601 (<.0001)
Race:	CCI	0.52	0.51, 0.53	---	---
White vs.	EI	0.54	0.53, 0.55	0.0223 (0.00505)	19.4633 (<.0001)
Non-White	**CDS**	**0.60**	**0.59, 0.61**	0.0859 (0.00585)	215.7498(<.0001)
	HRQL-CI_physical	0.58	0.57 , 0.59	0.0620 (0.00517)	143.9291(<.0001)
	HRQL-CI_mental	**0.60**	**0.59, 0.61**	0.0805 (0.00591)	185.4052(<.0001)
Healthcare behavior:	CCI	0.50	0.49, 0.52		
	EI	0.51	0.49, 0.52	0.0060(0.0065)	0.8423 (0.3587)
Better physician treatment or not	**CDS**	**0.52**	**0.51, 0.54**	0.0192 (0.0076)	6.3917 (0.0115)
	HRQL-CI_physical	0.51	0.49, 0.52	0.0028(0.0066)	0.1820 (0.6696)
	HRQL-CI_mental	0.51	0.50, 0.53	0.0095(0.0114)	0.7005 (0.4026)
Healthcare behavior:	CCI	0.52	0.51, 0.53	---	---
	EI	0.54	0.53, 0.55	0.0186 (0.0052)	12.9455 (0.0003)
Medication adherent or not	**CDS**	**0.56**	**0.55, 0.57**	0.0405 (0.0061)	44.4922 (<.0001)
	HRQL-CI_physical	0.53	0.51, 0.54	0.00755 (0.0054)	1.9747(0.1600)
	HRQL-CI_mental	0.50	0.49, 0.51	-0.0158 (0.0062)	6.4919 (0.0108)
Healthcare utilization:	CCI	0.63	0.61, 0.64	---	---
	EI	**0.65**	**0.63, 0.67**	0.0236(0.0074)	10.1769(0.0014)
High ER users or not	CDS	0.64	0.62, 0.66	0.0132(0.0088)	2.2584(0.1329)
	HRQL-CI_physical	0.64	0.62, 0.65	0.0101(0.0075)	1.8439(0.1745)
	HRQL-CI_mental	0.62	0.61, 0.64	-0.0043(0.0088)	0.234(0.6286)
Healthcare utilization:	CCI	0.61	0.59, 0.62	---	---
	EI	**0.62**	**0.61, 0.63**	0.0148 (0.0061)	5.8226(0.0158)

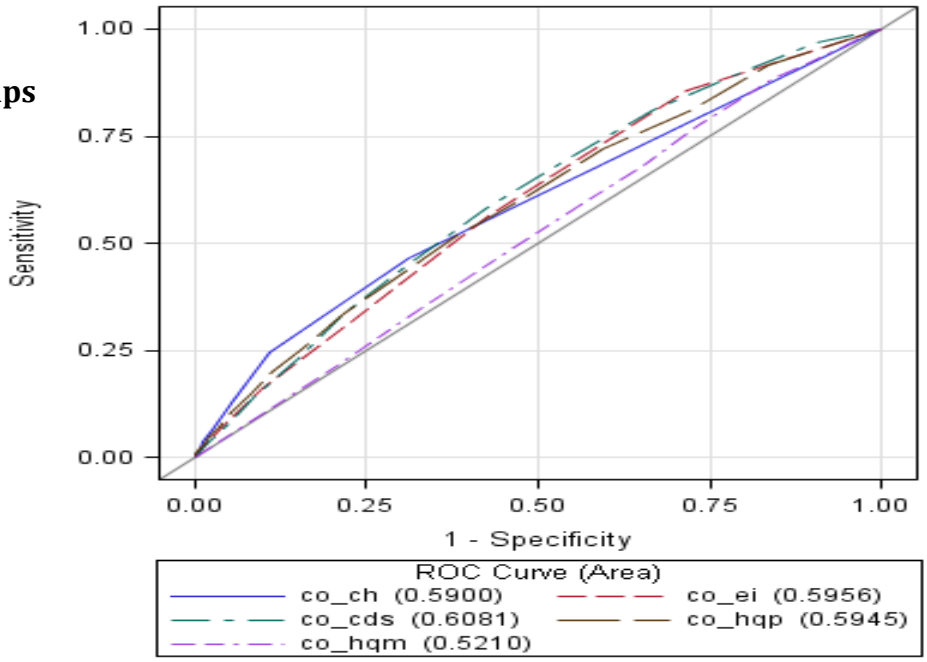
High Non-ER hospitalizations or not	CDS	0.61	0.59, 0.62	0.0020 (0.0072)	0.0772(0.7812)
	HRQL-CI_physical	**0.62**	**0.61, 0.64**	0.0155 (0.0063)	6.1328(0.0133)
	HRQL-CI_mental	0.61	0.60, 0.62	0.0031 (0.0074)	0.1807(0.6708)
Healthcare utilization: High outpatient visits or not	CCI	0.63	0.61, 0.65	---	---
	EI	**0.74**	**0.73, 0.76**	0.1155(0.0084)	188.0552(<.0001)
	CDS	0.72	0.71, 0.74	0.0974(0.0094)	107.1535(<.0001)
	HRQL-CI_physical	0.70	0.69, 0.72	0.0767(0.0087)	77.3803(<.0001)
	HRQL-CI_mental	**0.74**	**0.73, 0.76**	0.1172(0.0101)	135.6078(<.0001)
Healthcare costs: High total costs or not	CCI	0.64	0.62 , 0.66	---	---
	EI	**0.70**	**0.68, 0.71**	0.0572 (0.0083)	47.8362 (<.0001)
	CDS	0.65	0.64, 0.67	0.0142 (0.0101)	1.9856 (0.1588)
	HRQL-CI_physical	0.66	0.65, 0.68	0.0251 (0.0086)	8.4992 (0.0036)
	HRQL-CI_mental	0.66	0.64, 0.68	0.0197 (0.0103)	3.6657 (0.0555)
Healthcare costs: High diabetes care related costs or not	CCI	0.61	0.59, 0.63	---	---
	EI	**0.65**	**0.63, 0.66**	0.0348 (0.0087)	16.0365(<.0001)
	CDS	0.60	0.58, 0.62	-0.0141 (0.0101)	1.9608 (0.1614)
	HRQL-CI_physical	0.64	0.63, 0.66	0.0328 (0.0089)	13.6556 (0.0002)
	HRQL-CI_mental	0.60	0.59, 0.62	-0.0079 (0.0106)	0.5572 (0.4554)

CCI: Charlson Comorbidity Index; EI: Elixhauser Index; CDS: Chronic Disease Score, HRQL-CI: Health related Quality of Life Comorbidity Index; SE.: standard error; CIs: Confidence Limits

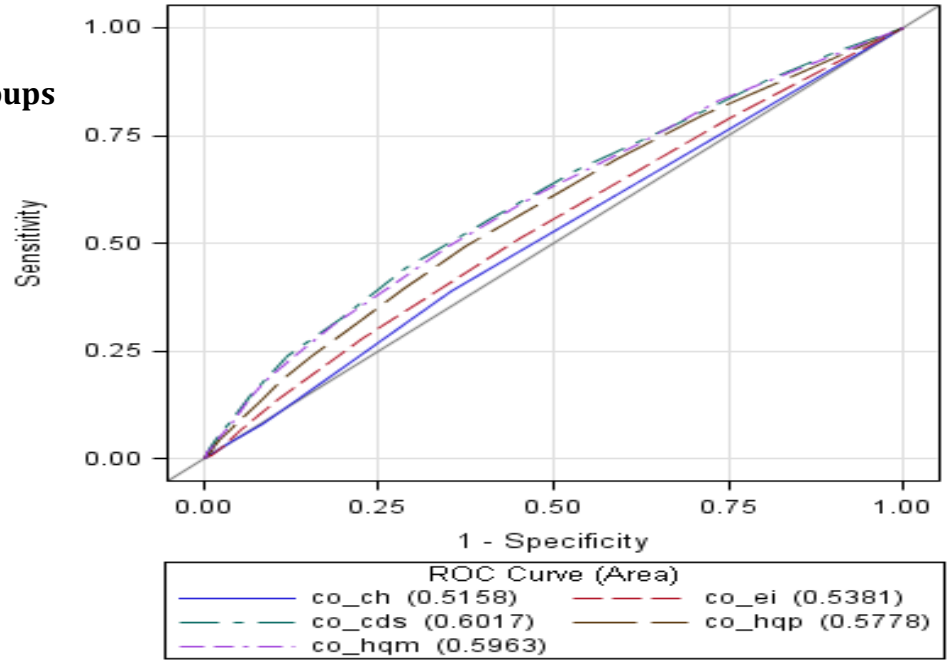
* A cutoff for age: 50 years old (younger defined as 18-49 years; older defined as 50-64 years); a cutoff for medication adherence: Medication Possession Ratio≥0.8;
a cutoff for high healthcare utilization: patients who used ≥90th percentile among study population;
a cutoff for high healthcare costs: patients who spent for diabetes care ≥90th percentile among study population

Figure 14: Area under the Receiver Operating Characteristic Curve for Comorbidity Index's Discriminating ability in Demographic subgroups

Age sugbroups



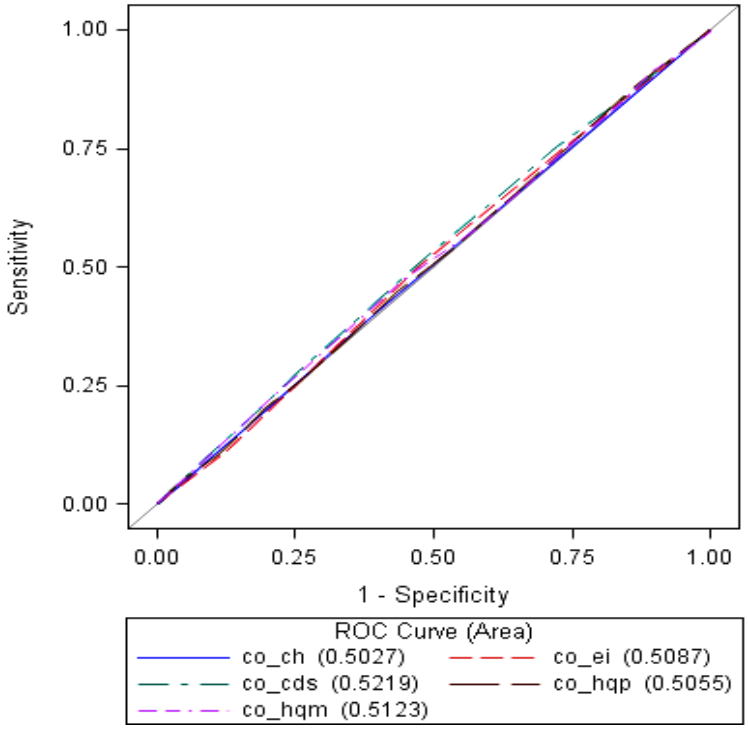
Racial sugbroups



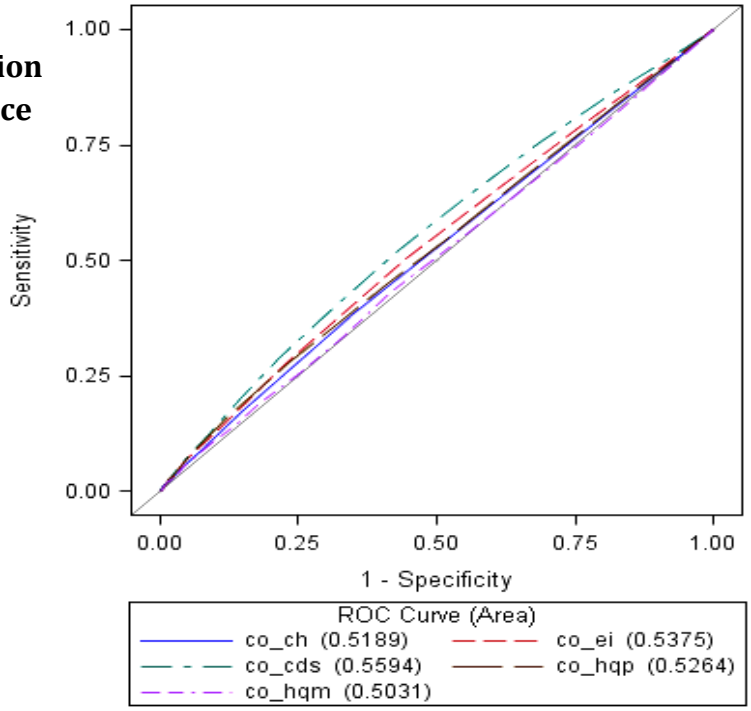
Co_ch: Charlson Comorbidity Index; Co_ei: Elixhauser Index
Co_cds: Chronic Disease Score
Co_hqp: Health related Quality of Life Comorbidity Index (HRQL-CI) (physical aspect);
Co_hqm: HRQL-CI (mental aspect)

Figure 15: Area under the Receiver Operating Characteristic Curve for Comorbidity Index's Discriminating ability in Healthcare related Behaviors

Physician treatment adherence



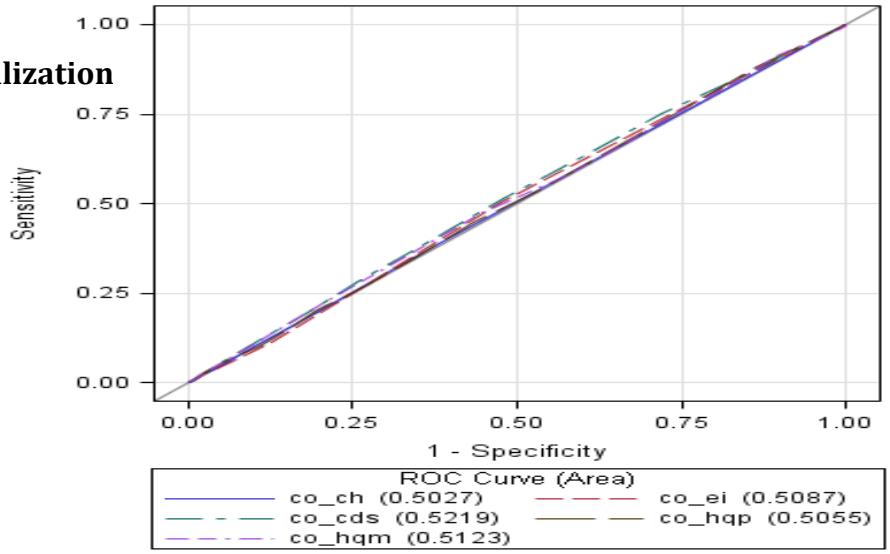
Patient medication adherence



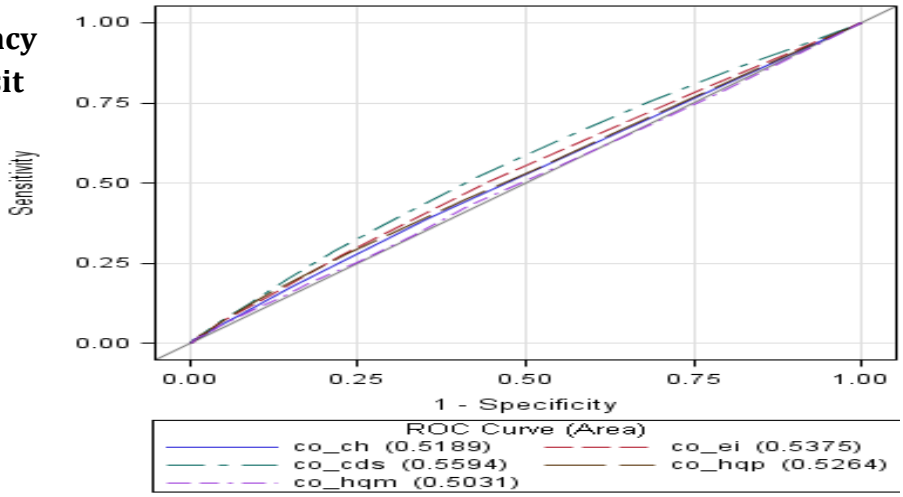
Co_ch: Charlson Comorbidity Index; Co_ei: Elixhauser Index
Co_cds: Chronic Disease Score
Co_hqp: Health related Quality of Life Comorbidity Index (HRQL-CI) (physical aspect);
Co_hqm: HRQL-CI (mental aspect)

Figure 16: Area under the Receiver Operating Characteristic Curve for Comorbidity Index's Discriminating ability in Healthcare Utilization

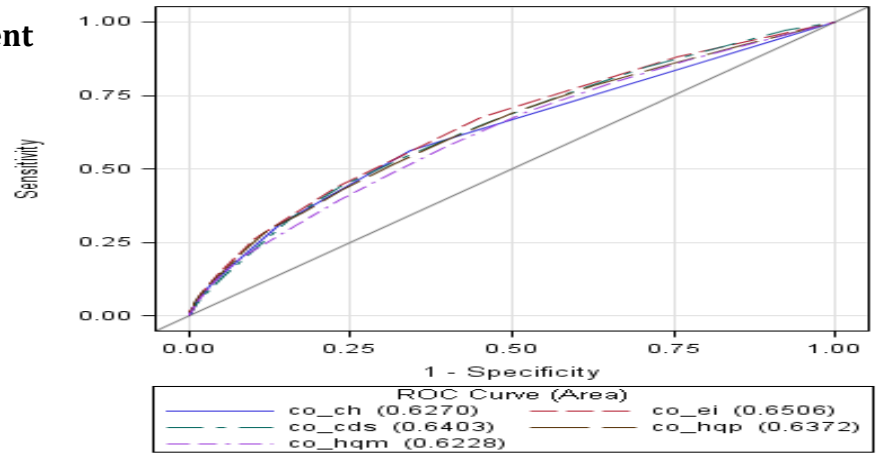
Hosptialization



Emergency room visit



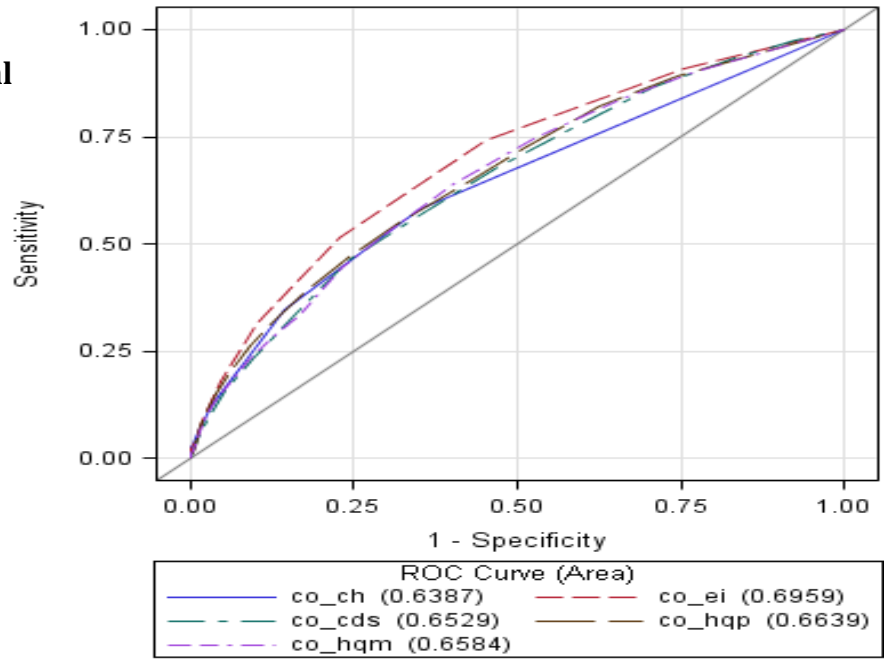
Outpatient visit



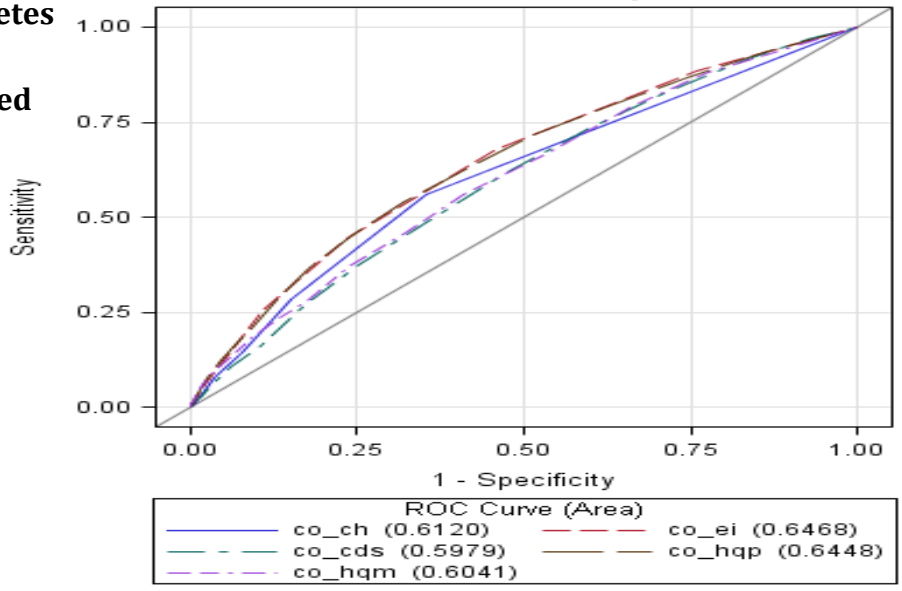
Co_ch: Charlson Comorbidity Index; Co_ei: Elixhauser Index Co_cds: Chronic Disease Score Co_hqp: Health related Quality of Life Comorbidity Index (HRQL-CI) (physical aspect); Co_hqm: HRQL-CI (mental aspect)

Figure 17: Area under the Receiver Operating Characteristic Curve for Comorbidity Index's Discriminating ability in Healthcare Expenditures

Total medical costs



Diabetes care related costs



Co_ch: Charlson Comorbidity Index; Co_ei: Elixhauser Index Co_cds: Chronic Disease Score
Co_hqp: Health related Quality of Life Comorbidity Index (HRQL-CI) (physical aspect);
Co_hqm: HRQL-CI (mental aspect)

Chapter

6. Dissertation Manuscript 3: Title: Dimensionality of Comorbidities for Heath related Quality of Life Comorbidity Index

Abstract

Background: This report presents the results of comorbidity patterns among 25 comorbidity candidates in the Health-related Quality of Life Comorbidity Index (HRQL-CI). The HRQL-CI consists of two lists of disorders for physical and mental aspects of HRQL outcome.

Methods: Using the MarketScan™ Medicaid database from 2003 to 2007, type 2 diabetes patients were targeted. Patterns of comorbidities were analyzed via confirmatory factor analyses for four subgroups: male, female, Black and White. Three models were compared: a uni-dimensional model, a 2-dimensional model in which 15 and 10 disorders represented physical and mental domains of comorbidities, respectively, a multi-dimensional model in which the dimensions were formed based on tetrachoric correlation matrices. Predictive performances of three comorbidity structures were assessed using regression analyses for four types of outcome data: physician treatment adherence, patient medication adherence, healthcare utilization and costs.

Results: 9,830 patients were included and majority of them was female (73%) and White (62%). A 7-factor pattern was noticeable in the correlations among comorbidity candidates across subgroups. Arrhythmias, heart failure, and ischemic heart disease formed a heart disease factor, rheumatoid arthritis, osteoarthritis and nontraumatic joint disorders formed a rheumatic disease factor, degenerative neurologic disorders and headaches formed a neurologic disease factor, esophageal disorders, gastric and duodenal ulcer formed a gastric disease factor, hepatitis,

biliary and liver disorders formed a liver disease factor, anxiety, depression, affective disorders, schizophrenia, other psychoses formed a mental disease factor. The 7-factor model provided best model fit across subgroups and better predictive performance across different healthcare outcomes and subgroups. Based on 7-factor model, individual comorbidity dimensions demonstrated differential impact for a given healthcare outcome and across different subgroups.

Conclusion: Accounting for underlying comorbidity dimensionality provides better risk adjustment and insightful information about differential impacts of different features of comorbidities for further developing efficient comorbidity management strategies.

Introduction

Measurement of comorbidity is particularly important in epidemiological and health services research. For controlling for confounding in epidemiologic analyses in which claims based data are used, comorbidity scores are useful tools. However, because studies of comorbidity or multimorbidity reveal that there is no consensus about how the co-occurrence of diseases should be measured [147], various approaches have been taken to characterize the combined burden of pre-specified diseases or conditions as a single measure on a scale. In general, comorbidities were commonly measured as a single summative score based on a list of candidate diagnoses and with or without weighting individual comorbidities to account for their differential impacts.

The simplest approach is to sum the number of diagnoses from a list of diagnosis candidates, which provides an ordinal comorbidity score [147-150]. This method has the advantage of conceptual simplicity and ease of data ascertainment. Some authors used ICD-9 codes to count the total number of comorbid conditions to examine the prevalence of comorbidity [147-149, 151], whereas others made up a list of carefully selected comorbid conditions and counted the number of these conditions present, by using medical records or ICD-9-CM codes, for the purpose of studying relationships between comorbidity and health related outcomes [33, 152, 153]. An example of such measures is the Functional Comorbidity index. It is an 18-item list of diagnoses, each of which is given 1 point if present, and the final score is simply a sum of the diagnosis present. It is aimed to predict health related outcomes specific to physical aspect of health-related quality of life [150].

However, because all diagnoses are scored equivalently, this assumes that all comorbid conditions have a similar effect and their overall impact on patients' lives is driven primarily by the number of conditions being managed. Such measures may capture the overall burden of illness, but they can not identify the characteristics of comorbid conditions that influence how patients and clinicians make decisions about the index disease treatments. This strategy ignores the fact that different diseases and their severity may affect the outcomes of interest differently.

Comorbidity indices first identify present comorbid conditions and subsequently apply weights or pathophysiologic severity ratings for these diseases. Some comorbidity measures weight the contributions of different diseases, depending on their role in the analytic relationship with an index disease. An example of such measures has been developed by Charlson (1987) [20]. The so-called Charlson Comorbidity Index (CCI) is a weighted index of comorbidity in which the weights were based on the observed association with 1-year mortality risk in a cohort of hospitalized patients. The index assigns a weight of 1 to 6, according to the risk of mortality, to each of the 19 defined comorbid conditions. The final comorbidity score is the sum of the weights for comorbid conditions a patient present. The weights can be taken directly from original index (called originally assigned weights) or generated from study own population by applying the same procedures for developing original weighting scheme into study population to get study population specific weight estimates (commonly called empirically driven weights). Previous research has shown that the predictive performance of comorbidity index was enhanced if investigators used study population driven weights, instead of the original weighting scheme, raising questions as to what weighting scheme to use [26, 40].

However, such a study specific weighting scheme may overly be customized to specific disease population and a given health outcome of interest, and, therefore, such a study weight based index will be less useful when applied into other settings (i.e., other index diseases and health related outcomes).

The disadvantage of a single summative comorbidity score, regardless of weighting of the individual conditions, is that it ignores potentially important relationships between diseases that might differ from their simple sum. For example, the interaction between chronic obstructive pulmonary disease and congestive heart failure might exceed the simple sum, whereas cardiovascular disease related to diabetes might be overweighed in an index that counts both independently. In the other words, these summative measures only assume an additive relationship for the included diseases, and, therefore, less address underlying etiologic associations between comorbidities. Also, these summed measures often force a linear

relationship with the ordinal scale across its entire range. A patient moving from zero to one comorbid disease could realize the majority of the comorbidity effect, with additional unit increases having a diminishing impact. Moreover, a single summative comorbidity score provides only a brief view about the impact of comorbidities as a whole but little known is how differently individual comorbidities influence on the outcome of interest.

One potential approach is to account for differential impacts of different comorbidities, rather than treating patient's illness burden as a summative score. This acknowledges underlying dimensionality of comorbidity and their differential impact on health outcomes. In order to examine thoughtful insights about differential impacts of comorbidities, disentangling the features of comorbidities is the first step. Piette and Kerr's conceptualization of typologies of comorbidities has provided an essential framework for studying how comorbidities of different characteristics have varying impacts on health outcomes [61]. One common classification is to define comorbidities as concurrent or discordant conditions[14]. This concept has been supported by research across different disease status study populations (i.e., hypertensive[387-391], schizophrenia[392], post-myocardial infarction[272], diabetes[45, 274], colon cancer[273] patients)and health outcomes (physician treatment behaviors[45, 274], patient medication adherence[387-392] and medical utilization[393, 394] and costs[198, 299, 395-399]). However, such a classification only built upon clinical adjustment about comorbid clinical representation to group comorbidities, and therefore, other approach may be needed to explore to study underlying comorbidity dimensionality and to confirm those classifications based on clinical judgments.

The Health-related Quality of Life Comorbidity Index (HRQL-CI) is a newer comorbidity measure, which consists of physical and mental parts of indexes to represent illness burden on one's physical and mental health, respectively. The comorbidities were grouped into physical and mental domain based on their

[14] Concordant conditions represent parts of the same overall pathophysiologic risk profile and are more likely to be focus of the same disease and self-management plan. Discordant conditions are not directly related in either their pathogenesis or management

predictive ability to physical and mental health outcome. Two lists of 20 and 15 clinical disorders were identified for physical and mental aspects of health-related outcomes, respectively. The weights were derived from the standardized beta coefficients in the regression model for HRQL outcomes. Compared to the CCI, this index has demonstrated greater explanatory power for the HRQL outcome data in the general population and a subset of asthma patients. [41]

One advantage of this index is that the impacts of physical and mental illness burden can be differential and therefore, managing comorbidities can be more effectively and specifically targeted influential part of illnesses. However, because physical and mental domains were generated on the basis of clinical adjustment, all comorbidity candidates were forced into these two domains. In this regard, the structure of these comorbidity candidates are still in need of detail investigation and physical and mental dimensionalities are needed to be evaluated further and confirmed in other types of population and settings.

Diabetes was seventh leading causes of morbidity and mortality in the United States in 2006[400]. Almost 17.9 million people had diagnosed diabetes in 2007, up from 8.5 million in 1995, and another 5.7 million people are though to live with undiagnosed diabetes today[401]. Roughly, 1.6 million new cases were diagnosed every year in people over 20 and prevalence has increased dramatically over the last 40 years often growing at double-digit rates[402]. This increased prevalence has been the primary reason for increased spending on diabetes over the last few decades, and has made diabetes one of the top 10 most expensive medical conditions in the US[403]. Medicaid covered about 15% of all individuals with diagnosed diabetes in the country in fiscal year 2003[48]. These beneficiaries account for a substantial portion of Medicaid program costs even though they are a relatively small percentage of this population [49].

Comorbidity among patients with diabetes was associated with considerable consequences for health care use, [2, 195, 196, 200] medical costs [2, 8, 192-201]. A strong correlation has been found between comorbidity and the use of hospital care (i.e., hospital admission)[2, 195, 196, 200], general practitioner care [200], and ambulatory specialist care [200]. Conversely, patients without comorbidity were

found to use little care [200]. Management of concurrent medical conditions with diabetes, such as cardiovascular diseases, accounted for approximately 76% of the projected $340 billion in the U.S. national expenditures for hospital inpatient care. However, with only 7% of inpatient days for this condition group attributed to diabetes disease itself, comorbidities, this constitutes the single largest contributor to the attributed medical cost of diabetes. Among concurrent comorbidities in patients with diabetes, cardiovascular diseases contributed major consumption of hospital inpatient care [201]. As diabetes-related complications or comorbid conditions develop and progress, disease management costs increase [198, 203]. Particularly in the Medicaid setting, diabetes patients tend to be older or disable with severe health complications, high healthcare demand and spending due to their illness burden. Therefore, considering the prevalence of comorbidities and their significant impact on healthcare outcomes, diabetes patients in the Medicaid setting could serve as comorbidity research candidate.

In present study, we used 25 diagnosis candidates in the HRQL-CI as an example to explore the dimensionality of comorbidities across different demographic subgroups in the Medicaid beneficiaries with diabetes and then to compare comorbidity scores based on our proposed comorbidity structure with commonly used summative comorbidity scores in predicting health outcomes. We assumed that comorbidity index which accounts for comorbidity dimensionality has better model fit to the data and predictive performance.

Method

Data source

This retrospective, observational, cohort study used the data from Thomson's MarketScan™ Medicaid dataset[355] from 2003 to 2007. MarketScan™ Medicaid dataset is a widely used source of data for many studies in different disease areas. It represents eight states of varying sizes across the United States. The database includes healthcare coverage eligibility and service use of individuals enrolled in state Medicaid programs from eight states. It includes outpatient and

inpatient services, prescription drug claims, long-term care, and enrollment data. In addition to standard demographic variables such as age and gender, the database also includes variables such as ethnicity, Medicare eligibility, and his or her provider's specialty.

We further classified study period into three specific intervals: (1) index drug identification period was the time window from 2004 to 2006. Within 24 months, the date when a patient's first OAD prescription claim occurred was defined as index date and the drug of the first OAD prescription is defined as index prescription. (2) Pre-index period was 12 months prior to the index date (starting from a patient's index date and look-back in time up to 12 months) and was used to verify continuous Medicaid eligibility as well as to identify baseline characteristics before starting any therapies. This also helped determine patients who did not have any OAD claims in this period and confirm a new start of the OAD medications in the index date. (3) Post-index period was12months after the index date (starting from a patient's index date and look-forward in time up to 12 months) and was used to ensure that patients had at least 12 months of follow-up period. Healthcare related behaviors (e.g., medication taking behavior) and outcomes (e.g., costs) were examined in this period.

Sample selection criteria

In the MarketScan™ database, individuals who satisfied all six following criteria were included in study cohort. (1) At least one outpatient or inpatient diagnosis of type 2 diabetes diagnosis based on the ICD-9-CM=250.0x-250.9x, where x=0 or 2. (2) Aged 18 to 64 years old at the index date. The reason for excluding individuals aged 65 years and above was that these people may be dual beneficiaries (Medicare and Medicaid enrollees) and therefore obtaining complete data on these patients may not be available. (3) Continuous enrollment in Medicaid in the pre- and post-index periods. The continuous enrollment criterion ensures that all study subjects had the same follow-up period, and therefore reduces bias due to failure to follow-up. (4) At least one filled prescription for OAD. (5) Drug naïve patients in pre-index period and newly starting OAD medication therapy during the index period window (2004-2006). Considering that newly treated patients

beginning their first course of medication are likely to have different medication use behaviors and responses to medication than are those already on a particular therapy, only newly started cases were included to understand the medication use behavior based on individuals who are naïve to OADs. (6) Patients with continuous medication therapy was defined by 2 following criteria: (a) Therapy without a lapse of> 60 days between date of days' supply expiration of any prescription fill and the subsequent claim date (days between end date of first fill and date of next fill), and (b) At least 2 prescription on the index medication.

Study variables

We focused on two aspects of healthcare outcomes, including healthcare related behaviors and outcomes. As guided by the Aday-Anderson's model for health care service utilization[64], three types of predictors for health outcomes were identified: predisposing, enabling and need factors. Healthcare outcomes were measured in post-index period and the predictors of healthcare outcomes were identified in pre-index period. Study variables were each specified as follows.

Healthcare related behaviors included physicians' adherence with diabetes treatment guideline and patient OAD medication adherence. Physician's treatment compliance score was estimated based on five recommended examinations by the American Diabetes Association (2005) [204], including at least two hemoglobin tests (HbA1c) per year, a cholesterol test per year, an eye examination per year, a mircoalbuminuria test per year and a foot examination per year. The final score was calculated as the sum of the number of recommended procedures completed. A person receiving more than 2 HbA1c tests was only given credit for it once. Except for the HbA1c test, a person having the same examination multiple times in the allotted time (e.g., more than one cholesterol screening within one year) was only given credit for it once. Treatment adherence scores range from zero (no recommended procedures performed) to five (all recommended procedures provided).

Medication adherence in this study was defined as patient's adherence to a new start of OAD, particularly focused on 3 common OAD as index drugs, including sulfonylureas, metformin, and thiazolidinediones and their fixed-dose regimens,

which were available in our study period, including Glucovance™ (glyburide plus metformin), Avplusamet™ (rosiglitazone plus metformin), Metaglip™ (glipizide plus metformin), and Actaoplus Met™ (pioglitazone plus metformin). Prescription refill patterns were used as a measure of medication adherence under the assumption that a prescription filled was a prescription taken. Medication possession ratio (MPR) was used to measure adherence. The observation period begins with the first date of dispensing (index date) and ends as the dispensing date of the last prescription within post-index period. Information on all filled prescriptions was extracted from the pharmacy claims file in the MarketScan™ Medicaid data. The formulations for computing the MPR were as follows. For monotherapy or fixed-dose regimen: MPR=total day's supply obtained/(date of the last claim—date of the first claim+day's supply of the last claim); for combination therapy (e.g., using more than one types of index drug or switching drugs): MPR=total day's supply obtained/n*(date of the last claim—date of the first claim+day's supply of the last claim) (n=no. of OAD combined, e.g., for dual therapy, n=2)

Regarding healthcare related outcomes, healthcare utilization included total number of hospitalization, emergency room (ER) and outpatient visits and healthcare expenditures included total healthcare cost and diabetes care related costs

Considering the predictors of healthcare outcomes, predisposing variables were patient's age, gender and race/ethnicity and enabling variables included three aspects of factors**:** access-related variables: healthcare insurance status and type of health plan, provider-related variables: type of provider (general practitioner vs. endocrinologist), and medication-related variables: number of therapeutic classes and total number of drugs. Need variables included diabetes disease severity and comorbidity. The present study defined diabetes severity by using 3 diabetes related complications as indicators: nephropathy, neuropathy, and retinopathy, and measured these complications in pre-index period. The propensity for healthcare utilization may increase with diabetes severity. The presence of each diabetic complication was recorded as a dichotomous variable. To avoid multicollinearity the

dummy variables were not summed up for each patient to obtain number of complications.

Comorbidity index chosen in the present study was the Health-related Quality of Life comorbidity index (HRQL-CI), which consists of two lists of 20 and 15 clinical conditions for physical and mental aspects of health-related outcomes, respectively. Each condition was assigned a point weight (ranging from 1 to 3), which was originally driven from the regression coefficients of individual comorbidities for physical and mental aspects of HRQL as outcome variables. The final HRQL-CI physical or mental aspect of score was each the sum of weights assigned to each condition a patient present. [41]

Statistical analysis

The descriptive statistics of population characteristics, including means, standard deviation, frequency and proportion, were performed for all study variables.

With considering the evidence that the presence of comorbidities varied in gender and race and as such contributed to the gender and racial disparities among diabetes patients,[364-366] we stratified study population by gender and race, in order to identify the patterns of comorbidities specific to these demographic subgroups. The following three analytical steps were performed within each subgroup.

1. **Assessment of dimensionality of comorbidities**

To assess comorbidities structure, confirmatory factor analysis (CFA) in the LISREL computer program (version 8.80; Scientific Software International Inc, Lincolnwood, III) was used as a mean to explore the correlations (i.e., patterns of comorbidity) among variables (i.e., comorbidities) by postulating that these correlations arose because of the influence of a smaller number of underlying, latent dimensions.

Specifically, tetrachoric correlation matrices created by the computer program PRELIS (version 2.2; Scientific Software International Inc, Lincolnwood, III), was assessed to obtain a preliminary understanding of how the individual comorbidities grouped together. The correlation matrices, together with clinical

judgments by investigators, provided an aid in grouping comorbidities for the purpose of the CFA. Then, tetrachoric correlation matrices and asymptotic covariance matrices computed by the PRELIS were used as input data in the CFA analyses.

Three types of comorbidity structure models were evaluated using the CFA. First, 1-factor model (uni-dimensional model) was evaluated in which all comorbidities were presumed to be indicators of a single, unitary propensity to experience comorbidities. Second, based on the original HRQL-CI index, which consists of physical and mental sub- parts of indexes, a 2-factor model was evaluated in which 15 comorbidities were presumed to reflect physical domain of comorbidities, and 10 comorbidities were presumed to reflect mental domain of comorbidities. This model was inspired by the concept that that the impacts of physical and mental illness burden on health outcomes can be differential. Third, a multiple dimensional model was evaluated in which the dimensions/factors were formed based on the correlation matrices and clinical judgements.

For each study subgroup, three competing CFA models (1, 2, multi-dimensional models) were assessed using the LISREL and compared. The model parameters were estimated using weighted least squares, a procedure that requires the aforementioned asymptotic covariance matrices. The weighted least squares procedure is appropriate for the analysis of patterns of comorbidity among the HRQL comorbidities because, it does not assume that the measured variables (i.e., comorbidities) have a joint multivariate normal distribution in the population. The fit of the models was evaluated using multiple fit indices: the X^2 goodness of fit statistic, the root mean square error of approximation (RMSEA), standardized root mean residual (SRMR), comparative fit index (CFI), and Akaike's Information Criterion (AIC). Each of these indices is commonly reported in CFA analyses, and each provides a complementary perspective on the fit of a CFA model. The X^2 value for a model indexes the discrepancy between the model-estimated and sample-derived correlations; smaller values result from better-fitting models. The RMSEA values of less than .08 were viewed as reflecting an adequate fit, with values less than .06 representing an excellent fit.[367] The SRMR indexes how far off the

model-estimated correlations are from sample-derived correlations (on average) and hence should be small for well-fitting models. [368] The CFI values close to one indicate good fit and the values around 0.9 indicate acceptable fit. There are no absolute cutoff on the AIC, but this index can be used to compare models, with lower values representing better fit.[369, 370] Conventional guidelines suggest that a difference of <6 in the AIC values between two models (either nested or non-nested)is small, 6–10 is substantial, and >10 is very substantial.[370]

2. **Construction of comorbidity scores**

Based on uni-dimensional model, two types of scores were estimated: a simple count summative score and empirically driven weight summative score. A simple count summative score was calculated by summing the presence of comorbidity candidates a person has. To obtain empirically driven weight summative score, we randomized study sample into two halves. Empirically driven weights were estimated based on strength of regression coefficient of individual comorbidity candidate for a given healthcare outcome from a half of study sample. Then, these empirically driven weights were applied into another half sample to obtain a summative weighted score by summing weights for comorbid conditions a person has.

Based on two-dimensional model, three types of scores were estimated. Like uni-dimensional model, we computed a simple count summative and empirically driven weight summative scores for each of two dimensions. Moreover, we computed a point weight summative score where the weights were originally assigned in the HRQL-CI index. A point weight score was estimated by summing point weights for comorbid conditions a person has.

Regarding multi-dimensional comorbidity structure, we treated each dimension as like a separate variable so one's illness burden was represented by a set of individual comorbidity scores, rather than a single summative score. For each comorbidity dimension, we had two types of scoring: a simple count score and factor loading based weight score. For a simple count score, each comorbidity dimension was treated as a dichotomous variable where a person having at least one comorbidity indicator for a given dimension was recorded as 1 and a person

with no comorbidity indicator for that dimension was recorded as 0. Moreover, we used factor loading as a weight for each comorbidity indicator. For a given comorbidity dimension, factor loading based weight score was the average of factor loadings for comorbidity indicators a person has.

3. Predictive performance of competing comorbidity models

To assess the performance of competing comorbidity models in predicting healthcare behaviors, utilization and costs, statistical analyses was selected based on the property of outcome data.

Physician treatment adherence scores, as a count variable, were modeled using standard Poisson regression model. We modeled medication adherence as a dichotomous variable based on a cutoff of the MPR values as 0.8 (MPR ≥ 0.8: being in adherent; MPR< 0.8: not adherent) and applied logistic regression analysis. In addition to comorbidity as independent variable of interest, the covariates in the models for physician and patient's adherence behaviors were predisposing and enabling factors, and three diabetes severity indicators. Zero-inflated binomial regression analysis was applied for each type of healthcare utilization data in post index period. Medical expenditure data were considerably skewed to right. Log-linear and generalized linear models (GLMs) are two commonly used methods of analyzing healthcare expenditure data, particularly for dealing with skewed data. Manning and Mullahy [360] describe the criteria necessary for choosing between the two. The Park test for family selection in a GLM [360] indicated that a GLM model with gamma family was most appropriate for this analysis. The covariates in the models for healthcare utilization (or costs) outcome data were predisposing, enabling and need factors, healthcare related behaviors (physician treatment adherence and patient medication adherence), and healthcare utilization (or costs) in pre-index period.

The likelihood ratio (LR) for goodness of fit, deviance and adjusted pseudo R^2 were reported as statistical evidence of model fit of each model, compared to its nested intercept only model. The Akaike's information criterion (AIC) and Bayesian information criterion (BIC) are two common information criterion measures used to

compare non-nested models and the model with the lowest AIC or BIC value is the best model.

Results

Characteristics of study population

Total sample size was 9,832, where majority of study population were female (73%) and White (62%). Compared to female population, males received better physician treatment, adhered to diabetes medication, and had higher numbers of hospitalization and emergency room visit, and higher medical spending, but less outpatient visits. Also, compared to black patients, white patients received better physician treatment, better adhered to diabetes medication, and had higher numbers of hospitalization and outpatient visit, and total medical spending, but had lower emergency room visits and spending in diabetes related care. (table 24)

Regarding the prevalence of comorbid conditions, compared to male subgroup, female subgroup had relatively higher prevalence of degenerative neurologic disorders (male vs. female: 31.04% vs. 40.85%), osteoarthritis & nontraumatic joint disorders (male vs. female: 26.47% vs. 34.68%), and spinal column disorders (male vs. female: 27.01% vs. 31.62%); males had relatively higher prevalence of hypertension (male vs. female: 57.10% vs. 48.61%), ischemic heart disease (male vs. female: 21.52% vs. 12.60%), and obstructive pulmonary disease (male vs. female: 19.05% vs. 16.84%) when compared to females. Moreover, compared to black patients, white patients had relatively higher prevalence of degenerative neurologic disorders (white vs. black: 39.99% vs. 35.40%), spinal column disorders (white vs. black: 35.30% vs. 22.25%), and osteoarthritis & nontraumatic joint disorders (white vs. black: 35.18% vs. 28.07%); when compared to white patients, black patients had relatively higher prevalence of hypertension (white vs. black: 47.91% vs. 55.78%). (table 25)

Tetrachoric correlations among comorbidities

Tetrachoric correlations among comorbidities were computed for each subgroup. A 6-factor pattern was noticeable in these correlations in male subgroup

(table 26). The correlations among anxiety & depression, affective disorders, schizophrenia, other psychoses, between rheumatoid arthritis & rheumatic disorders and osteoarthritis & nontraumatic joint disorders, between degenerative neurologic disorders and headaches, between esophageal disorders and gastric & duodenal ulcer, between hepatitis and biliary and liver disorders, between anxiety & depression and affective disorders, schizophrenia, other psychoses were moderately high.[15]

A 7-factor pattern was noticeable in these correlations in female, white and black subgroups (table 27, 28 and 29). The correlations among anxiety & depression, affective disorders, schizophrenia, other psychoses, between obstructive pulmonary disease and asthma, between rheumatoid arthritis & rheumatic disorders and osteoarthritis & nontraumatic joint disorders, between degenerative neurologic disorders and headaches, between esophageal disorders and gastric & duodenal ulcer, between hepatitis and biliary and liver disorders, between anxiety & depression and affective disorders, schizophrenia, other psychoses were moderately high.

Multi-dimensional comorbidity structure and model fit among three types of comorbidity structures

Fit indices of the three models of comorbidity structures were summarized in table 30. The results of structure analyses were strikingly similar across different subgroups, showing smallest RMSEA and SRMR, largest CFI and smallest AIC values based on the multi-dimensional comorbidity structure, compared to those based on either uni- or two-dimensional structure. All these findings demonstrated strong evidence for the superiority of the multi-dimensional comorbidity structure.

[15] Initially, the male subgroup had seven factors which included lung disorder that was assumed being predicted by obstructive pulmonary disease and asthma. The correlation between these two disorder indictors were moderately high (0.42), but these two indicators had different magnitudes of correlations with the indicators for other factors. For example, the correlation between asthma and heart failure was 0.08, while the correlation between obstructive pulmonary disease and heart failure was0.29; also, the correlation between asthma and ischemic heart disease was 0.08, while the correlation between obstructive pulmonary disease and ischemic heart disease was0.36. as a result, the software can not find the solution to convergence for estimation. We have tried to fix this by trying using different start values and adjusting the numbers of iterations, but all can not work. Therefore, we kept obstructive pulmonary disease and asthma as separated indicator to predict each underlying disorder, rather than in one dimension which represents lung disease.

Figure 18 depicted the results for factor loadings for male subgroup. High factor loadings were found for "neurologic diseases" (0.96-0.84); estimates for "gastric disease" (0.43-0.57) were low. In the figure 2 for female population, high factor loadings were also found for "neurologic diseases" (0.77-0.99); estimates for "heart disease" (0.56-0.67) were low.

Moreover, with considering some comorbid conditions that are prevalent and important in this particular study population, the conditions that were prevalent in a given study subgroup but not chosen in the multi-dimensional CFA model were selected to be a single indicator for its representing disease. In each subgroup, whole comorbidity structure consisted of two parts of dimensions: multi-indicator dimensions and single-indicator dimensions. For male population, in addition to six-multi-indicator dimensions (as shown in figure 1), three single-indicator dimensions selected were spinal column disorders (prevalence: 27.01%, table 25), vision disorders (prevalence: 12.36%, table 25) and epilepsy and convulsions (35.35% of male having this in table 25). In the female, in addition to seven-multi-indicator dimensions (as shown in figure 19), five single-indicator dimensions selected were spinal column disorders (prevalence: 27.01%, table 25), thyroid disorder (prevalence: 13.88%, table 25), vision disorders (15.42% of female having this in table 25), epilepsy and convulsions (prevalence: 37.94%, table 25), and anemia (prevalence: 9.71%, table 25).

The predictive performances of three types of comorbidity structures

In male subgroup, although all models with different comorbidity structures and weighting schemes fit medication adherence outcome data well, with given evidence of the insignificant Hosemer & Lemeshow test, the models based on 6-dimensional comorbidity structure had better model fit, with regard to the evidence of largest LR, smallest deviance, largest adjusted R^2 and smallest AIC values. Also, across different healthcare outcomes of interest, including physician treatment adherence (table 31), healthcare utilization (table 32), and costs (table 33), all results demonstrated the superiority of predictive performance of the models based on 6-dimensional comorbidity structure compared to uni- and two-dimensional structure.

In female subgroup, better predictive performances of the models based on 7-dimesnional comorbidity structure were also found in the outcomes of healthcare related behaviors (table 34), healthcare utilization (table 35) and costs (table 36).

When comparing between multi-dimensional comorbidity structure based scores without weights (Simple count scores for each individual dimension) and with factor loading based weights, similar predictive performance were observed in different study subgroups and healthcare outcomes of interest.
(in fact, when data split by race, we also found better performance of the models based on 7-dimensional comorbidity structure in predicting different healthcare outcomes of interest in both White and Black subgroups. These results and tables are available on request)

The differential impact of individual comorbidity dimension

Using factor loading based weighted scores as an example, our results demonstrated differential impacts of comorbidity dimensions in healthcare outcomes and across different study subgroups. First, in male group, lung diseases, neurologic diseases and vision disorders had negative impact their antidiabetic medication adherence, while rheumatic disorders and neurologic disorders had statistically significant, negative impact on physician treatment adherence. For the female, neurologic diseases had negative impact on patient anti-diabetic medication, while liver, thyroid, vision disorders and anemia had negative impact on physician treatment adherence. (table 37)

For healthcare related utilization as outcomes of interest, in male group, lung diseases were positively associated with the number of hospitalization, heart diseases, mental disorders epilepsy and convulsions were positively associated with outpatient visits. In the female subgroup, lung disorders and anemia were positively associated with hospitalization, lung diseases was positively associated with emergency room visits, and heart, lung, rheumatic, mental, spinal column, vision disorders and epilepsy and convulsions were positively associated with outpatient visits. (table 38)

For healthcare related costs as outcomes of interest, in male group, heart and neurologic diseases were positively associated with total medical costs, heart, lung,

neurologic, vision disorders and epilepsy and convulsions were positively associated with diabetes care related costs. In female group, lung and mental diseases were positively associated with total medical costs, lung disorders were positively associated with diabetes care related costs. (table 39)
(When data split by race, we also found differential impacts of comorbidity dimensions across different healthcare outcomes in the White and Black subgroups.)

Discussion

This study provided a novel contribution towards understanding the structure of comorbidities. Our findings had important implications for comorbidity measurement, the management of comorbidities and genetic etiology. The implication for the comorbidity measurement stem from the findings that comorbidity scores based multi-dimensional comorbidity structure demonstrated best fit to healthcare outcomes data across subsamples stratified by gender and race. This implied that multi-dimensional comorbidity structure could be a more valid approach to represent illness burden in the context of Medicaid receipts with diabetes. Moreover, compared to commonly approach that all diagnoses were presumed to be indicators of a single, unitary propensity to experience comorbidities, multi-dimensional comorbidity model, in which the dimensions were formed based on the correlations between disorders and clinical judgements, demonstrated improved predictive performance of comorbidity measure across critical healthcare outcomes and demographic subgroups. This implied that comorbidity measurement accounting for comorbidity dimensionality, which represents underlying characteristics of grouped disorders, could provide better risk adjustment and prognostic prediction for healthcare service research. In this regard, comorbidity research on should move beyond relying on simple counts of diagnoses or other uni-dimensional scores as a means of capturing the effect of comorbidity on patient's healthcare outcomes.

Second, disentangling comorbidity dimensions provides informative insights for the management of comorbidities. As built upon multi-dimensional structure,

differential impacts of different characteristics of comorbidities in healthcare outcomes can be evaluated and therefore, more efficient and specific approach that targets influential comorbidities for a given outcome could be developed. For example, based on our findings, neurologic and vision disorders had negative impact on male patients' OAD medication adherence. This implied that these disorders could focus patient attention away from diabetes self-management and would therefore be associated with poor OAD prescription refill. In this regard, tailoring approach based on the types of comorbidities could be developed where diabetics patients with neurologic or vision diseases may be in need to be intervened for improving their OAD medication adherence.

Also, our results showed that liver, thyroid and vision disorders in diabetics female patients could strain physicians'' ability to adhere diabetes quality of care guideline in terms of prescribing recommended diabetes disease examinations, implying that these disorders may place competing effects on physicians' managing diabetes disease. So, for instance, continuous education for physicians could more emphasize on the approach of co-managing diabetes with these disorders. Moreover, regarding medical resource allocation, understanding differential impacts of individual comorbidity dimensions is also important for identifying patients who are likely to have high healthcare demand and spending. For example, according to our findings, compared to other types of comorbidities, diabetic male patients with heart diseases were more likely to have more hospitalization admissions, while those with mental disease tended to have high outpatient visits. Also, heart diseases may place diabetes patients, particularly the male, at risk of high medical spending.

However, some weaknesses of this study should be kept in mind when interpreting these results. First, due to analyses based on claims data, the information on services not billed to the insurance system was not available (patients may receive treatment that is not submitted to their health plan for reimbursement and thus not included in claim data). Second, correct categorization of insurance database information depends on correct codlings by clinicians and other medical staff. The accuracy of diagnostic coding can not be evaluated in a claims-based study. Also, in coding each ICD-9-CM claims-based measurement,

there exists the possibly that ruled out diagnoses that were assigned for billing purposes were misclassified as existing comorbidities.[76] Third, data on comorbidities were limited to conditions coded on medical claims within the time frame studies. And, comorbidity candidates only were based on the HRQL comorbidity index and therefore may not represent the most prevalent comorbidities in Medicaid patients with diabetes. Fourth, caution should be used when generalizing results beyond the study population of continuously enrolled type 2 diabetes patients 18 to 64 years from Medicaid setting. Also, our sample was predominantly female and White. Additional studies should compare and validate these measures for health service use outcomes among other patient populations.

In conclusion, the present study provided a good starting-point towards understanding how comorbidity candidates can be organized and supported the importance of accounting for comorbidity dimensionality in comorbidity measurement and the management of comorbidities. Our main finding that comorbid burden was better reflected by multi-dimensional, rather than uni-dimensional, could serve as a preliminary evidence for comorbidity research. Also, our finding implied that research focused the impact of illness burden on patients' outcomes needs to move beyond familiar approach that relied on a single summative count or weighted score, because such an uni-dimensional comorbidity score less fit to healthcare outcome data and had less predictive validity for healthcare outcomes, particularly in the context of Medicaid setting. Moreover, our multi-dimensional comorbidity model provided a promising avenue for the broadest level of organization of comorbidity candidates in the HRQL-CI and for research aimed to evaluate impacts of different characteristics of individual comorbidity dimensions on healthcare outcomes.

Further research should be carried out using the concept of our study approach to understanding comorbidity dimensionality, including prevalent comorbidity candidates in a given study population, and validating our findings in other disease types of patients, other healthcare settings, and different data sources (i.e., medical records). Also, since our multi-dimensional comorbidity model was only a first-order factor structure, further research could investigate whether the

pattern of comorbidity candidates could even be better reflected by a hierarchical factor structure (i.e., second-order model), in terms of better predictive performance in healthcare outcomes.

Table 24: Characteristics of Study Subgroups (n=9,830)

Subgroups	**Men**	**Female**	**White**	**Black**
Characteristics	Mean (S.D.)	Mean (S.D.)	Mean (S.D.)	Mean (S.D.)
Healthcare related behaviors	**2.58** (1.09)	2.46 (1.11)	**2.53** (1.07)	2.42 (1.15)
Physicians' treatment adherence to diabetes care (score: 0-5)				
Patient's adherence to diabetes medication (MPR: 0-1)	**0.83** (.21)	0.80 (.23)	**0.82** (.21)	0.77 (.24)
Healthcare utilization (no. per year)				
Hospitalization	**0.38** (.94)	0.35 (.99)	**0.37** (.93)	0.34 (1.05)
No. of emergency room visits	**0.25** (.74)	0.21 (.79)	0.22 (.73)	**0.23** (.85)
No. of outpatient visits	27.96(40.6)	28.55 (38.55)	**30.02** (39.37)	25.68 (38.48)
Healthcare costs (per year)				
Total costs	**10219.95** (29751.63)	8558.75 (27917.39)	**9175.75** (32078.25)	8699.65 (20968.12)
Diabetes care related costs	**2836.90** (11627.72)	2055.33 (9371.75)	2075.59 (9672.66)	**2571.00** (10571.6)

MPR: medication possession ratio

Table 25: Distribution of Comorbidities among Study Subgroups

Subgroup	Gender				Race			
	Men (n=2,184)		Female (n=6,046)		White (n=5,139)		Black (n=3,096)	
Comorbidity	n	%	n	%	n	%	n	%
Paralysis (PAL)	39	1.79	62	1.03	56	1.09	45	1.45
Rheumatoid arthritis & rheumatic disorders (RAD)	44	2.01	173	2.86	158	3.07	59	1.91
Heart failure (HTF)	224	10.26	808	13.36	710	13.82	322	10.40
Systemic lupus erythematosus (SLE)	9	0.41	51	0.84	32	0.62	28	0.90
Ischemic heart disease (IHD)	470	**21.52**	762	12.60	835	16.25	397	12.82
Osteoarthritis & nontraumatic joint disorders (OJD)	578	26.47	2097	**34.68**	1808	**35.18**	869	28.07
Hepatitis (HPT)	175	8.01	323	5.34	338	6.58	160	5.17
Degenerative neurologic disorders (DND)	678	31.04	2470	**40.85**	2055	**39.99**	1096	35.40
Peripheral & central vascular diseases (PCV)	83	3.80	175	2.89	183	3.56	76	2.45
Spinal column disorders (SCD)	590	27.01	1912	**31.62**	1814	**35.30**	689	22.25
Obstructive pulmonary disease (OPD)	416	**19.05**	1018	16.84	1096	21.33	338	10.92
Gastric & duodenal ulcer (GDU)	72	3.30	251	4.15	210	4.09	113	3.65
Hypertension (HPN)	1247	**57.10**	2939	48.61	2462	47.91	1727	**55.78**
Asthma (ATM)	159	7.28	965	15.96	743	14.46	381	12.31
Arrhythmias (ARM)	265	12.13	678	11.21	603	11.73	340	10.98
Esophageal disorders (EPD)	297	13.60	991	16.39	949	18.47	339	10.95
Thyroid disorders (TYD)	107	4.90	839	13.88	680	13.23	267	8.62

Vision disorders (VSD)	270	12.36	932	15.42	807	15.70	397	12.82
Anxiety & depression (ADP)	315	14.42	1121	18.54	1107	21.54	330	10.66
Affective disorders, schizophrenia, other psychoses (ADS)	340	15.57	1248	20.64	1182	23.00	407	13.15
Hiv infection (HIV)	27	1.24	35	0.58	16	0.31	46	1.49
Epilepsy, convulsions (ECV)	772	35.35	2294	**37.94**	2105	40.96	962	31.07
Headaches (HAD)	243	11.13	1377	22.78	1049	20.41	571	18.44
Biliary and liver disorders (BLD)	756	34.62	2321	**38.39**	2093	40.73	985	31.82
Anemia (ANA)	135	6.18	587	9.71	359	6.99	363	11.72

Table 26: Tetrachoric Correlations among Dimensional Comorbidity Indicators in Men Subgroup

	ARM	HTF	IHD	RAD	OJD	DND	HAD	EPD	GDU	HPT	BLD	ADP	ADS
ARM	1												
HTF	0.35	1											
IHD	0.33	0.38	1										
RAD	0.01	-0.03	-0.02	1									
OJD	-0.01	0.1	0.04	0.29	1								
DND	0.15	0.13	0.15	0.08	0.23	1							
HAD	0.1	0.26	0	-0.01	0.15	0.77	1						
EPD	0.04	0	0.07	0.24	0.15	0.12	0.16	1					
GDU	-0.12	0.04	-0.01	0.05	0.07	0.04	0.13	0.41	1				
HPT	0	0.01	-0.08	0.21	0.06	0.21	0.02	0.16	-0.05	1			
BLD	0.17	0.12	0.12	0.09	0.11	0.51	0.11	0.17	-0.08	0.42	1		
ADP	-0.11	-0.1	-0.08	0.03	0.1	0.16	0.15	0.04	0.12	-0.01	0.08	1	
ADS	0	-0.13	-0.12	0.04	0.06	0.11	0.16	0.04	0.01	0.13	0.05	0.46	1

Table 27: Tetrachoric Correlations among Dimensional Comorbidity Indicators in Female Subgroup

	ARM	HTF	IHD	OPD	ATM	RAD	OJD	DND	HAD	EPD	GDU	HPT	BLD	ADP	ADS
ARM	1														
HTF	0.2	1													
IHD	0.37	0.28	1												
OPD	0.14	0.26	0.23	1											
ATM	0.07	0.18	0.11	0.37	1										
RAD	0	-0.03	0.03	0.1	0.04	1									
OJD	0.04	0.09	0.06	0.15	0.13	0.32	1								
DND	0.16	0.25	0.15	0.1	0.13	0.1	0.2	1							
HAD	0.03	0.54	0.02	0.1	0.13	-0.04	0.11	0.74	1						
EPD	0.01	0.11	0.05	0.12	0.09	0.09	0.17	0.16	0.16	1					
GDU	0.07	0.05	0.13	0.01	-0.01	-0.05	0.06	0.06	0.09	0.32	1				
HPT	0.04	0.05	0.04	0.07	0.02	0.05	0.02	0.17	0.1	0.13	0.13	1			
BLD	0.16	0.11	0.16	0.1	0.06	0	0.13	0.52	0.11	0.17	0.17	0.39	1		
ADP	0.09	0.15	0.03	0.12	0.06	-0.05	0.1	0.15	0.21	0.1	-0.03	0.05	0.09	1	
ADS	-0.02	0.08	-0.03	0.07	0.08	-0.12	0.08	0.1	0.1	0.11	0.06	0.07	0.07	0.47	1

Table 28: Tetrachoric Correlations among Dimensional Comorbidity Indicators in White subgroup

	ARM	HTF	IHD	OPD	ATM	RAD	OJD	DND	HAD	EPD	GDU	HPT	BLD	ADP	ADS
ARM	1														
HTF	0.21	1													
IHD	0.37	0.26	1												
OPD	0.13	0.27	0.23	1											
ATM	0.04	0.17	0.02	0.33	1										
RAD	0	0.01	0	0.11	0.01	1									
OJD	0.01	0.13	0.01	0.13	0.14	0.29	1								
DND	0.14	0.24	0.11	0.11	0.17	0.07	0.22	1							
HAD	0.02	0.54	-0.03	0.1	0.16	-0.05	0.15	0.72	1						
EPD	0.03	0.10	0.05	0.11	0.1	0.14	0.16	0.17	0.17	1					
GDU	0	0.08	0.12	0.05	0.02	-0.03	0.09	0.07	0.1	0.33	1				
HPT	-0.02	0.00	0	0.04	-0.02	0.12	0.04	0.18	0.06	0.17	0.1	1			
BLD	0.16	0.11	0.1	0.09	0.07	0.03	0.11	0.53	0.12	0.17	0.12	0.42	1		
ADP	0.02	0.12	-0.03	0.08	0.07	-0.03	0.12	0.16	0.24	0.08	0	-0.01	0.07	1	
ADS	-0.05	0.06	-0.09	0.03	0.11	-0.07	0.1	0.11	0.13	0.1	0.05	0.09	0.07	0.43	1

Table 29: Tetrachoric Correlations among Dimensional Comorbidity Indicators in Black subgroup

	ARM	HTF	IHD	OPD	ATM	RAD	OJD	DND	HAD	EPD	GDU	HPT	BLD	ADP	ADS
ARM	1														
HTF	0.3	1													
IHD	0.31	0.34	1												
OPD	0.14	0.22	0.24	1											
ATM	0.09	0.17	0.1	0.43	1										
RAD	0.01	-0.15	0	0.07	0.01	1									
OJD	0.04	0.01	0.06	0.12	0.18	0.35	1								
DND	0.17	0.21	0.16	0.05	0.12	0.15	0.2	1							
HAD	0.07	0.37	0	0.04	0.15	0.04	0.09	0.8	1						
EPD	-0.04	0.02	-0.02	0.06	0.09	0.01	0.15	0.09	0.14	1					
GDU	0.09	-0.03	0.01	-0.07	-0.06	-0.03	0.01	0.04	0.1	0.36	1				
HPT	0.11	0.09	0.01	0.11	0.08	-0.04	-0.04	0.14	0.05	0	0.03	1			
BLD	0.16	0.12	0.18	0.03	0.1	-0.04	0.12	0.49	0.11	0.12	0.09	0.33	1		
ADP	0.1	0	-0.02	0.02	0.05	-0.11	0.03	0.13	0.11	0.02	0.02	0.09	0.09	1	
ADS	0.04	-0.03	-0.05	0.01	0.04	-0.25	0	0.1	0.07	0.02	0.06	0.03	0.01	0.52	1

Figure 18: Best-Fitting Model for Male Subgroup: Six-Dimension Comorbidity Model

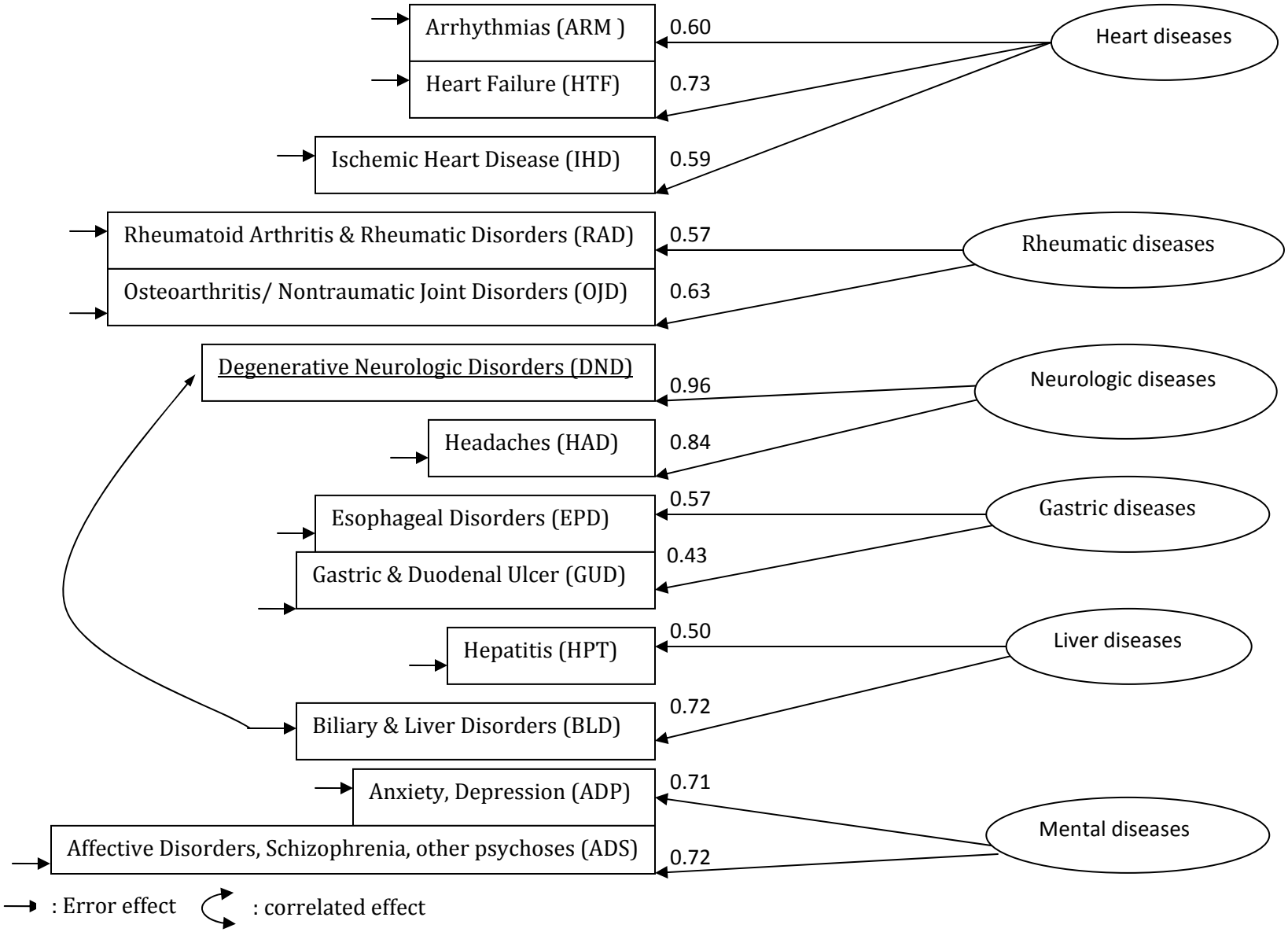


Figure 19: Best-Fitting Model for Female Subgroup: Seven-Dimension Comorbidity Model

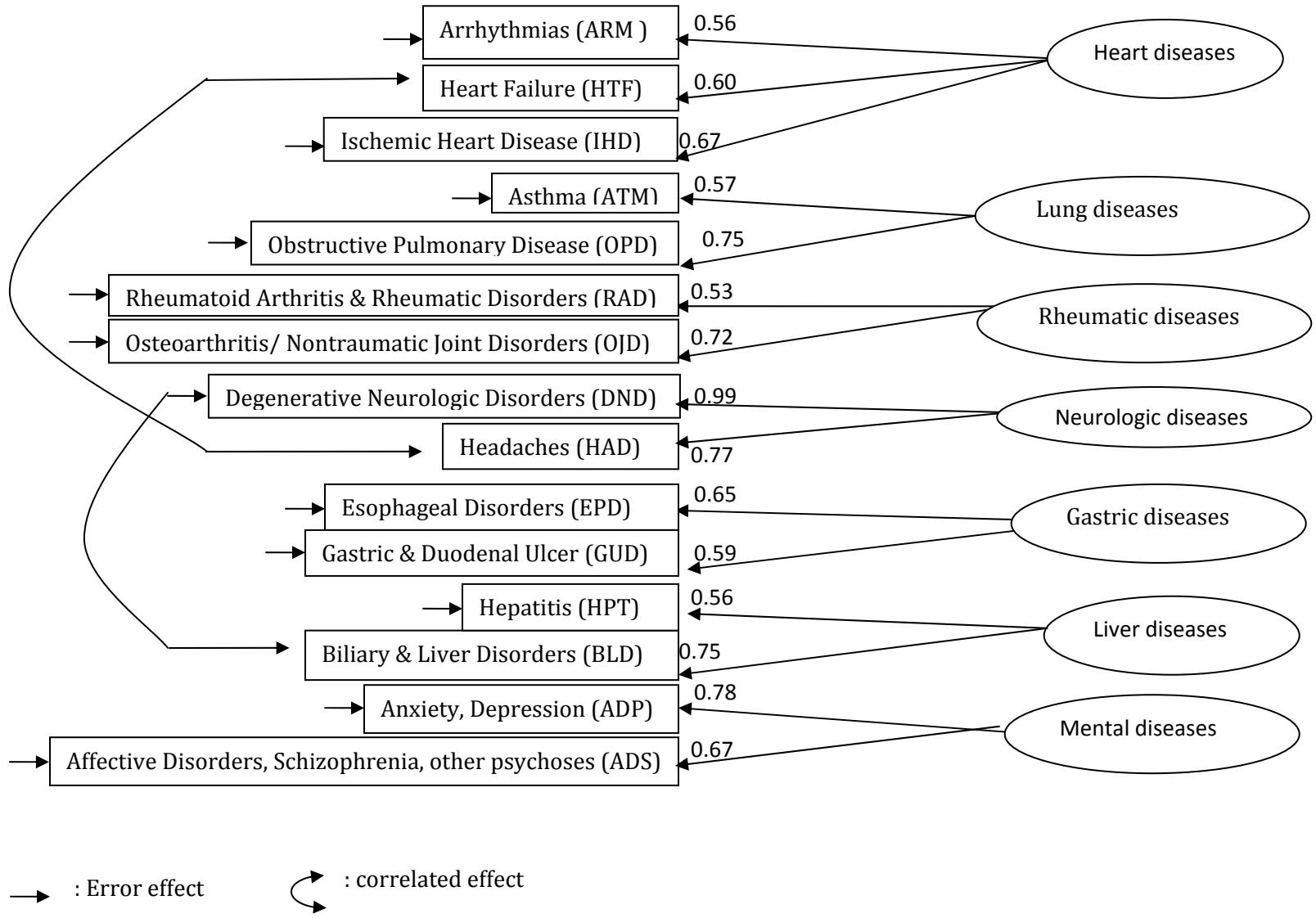


Figure 20: Best-Fitting Model for White Subgroup: Seven-Dimension Comorbidity Model

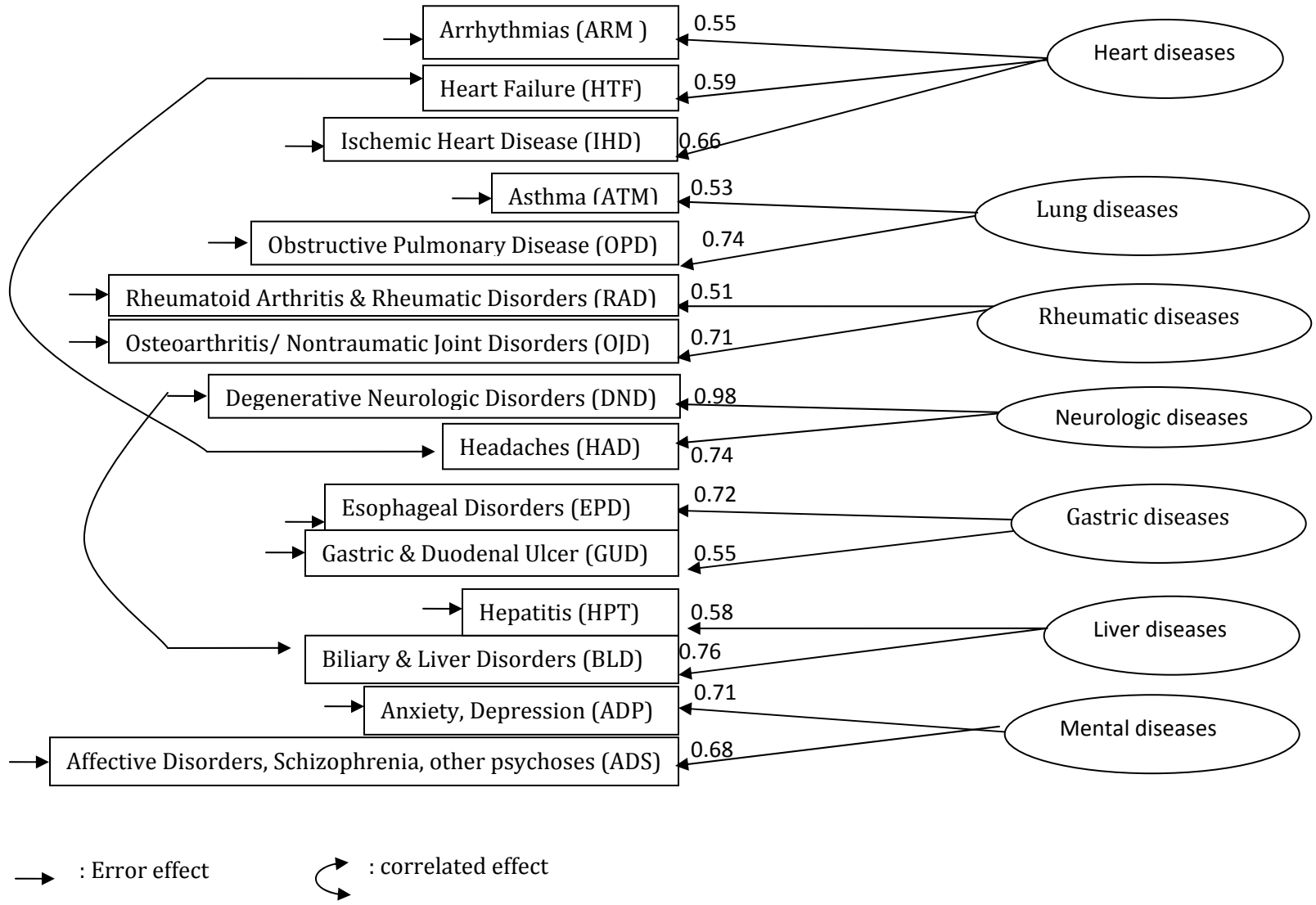


Figure 21: Best-Fitting Model for Black Subgroup: Seven-Dimension Comorbidity Model

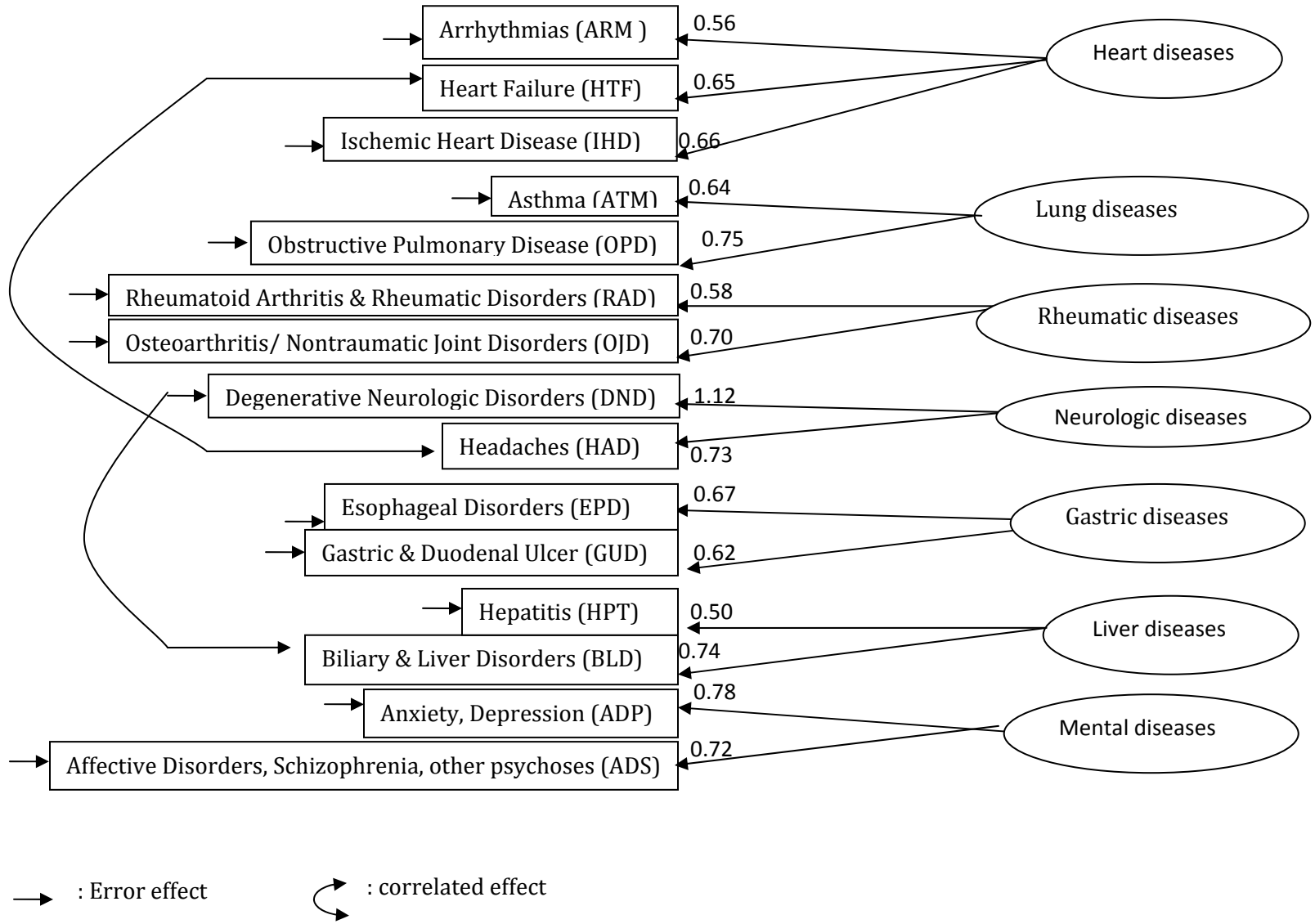


Table 30: Model Fit Indices for Three Types of Comorbidity Structure in Study Subgroups

Fit indices (criteria) / Subgroup	Factors	X^2 (p≥.05)	RMSEA (≦.06)	SRMR (≦.08)	CFI (~0.95)	AIC (small)
Male	1	4615.86 (p=.0,df=64)	.057	0.14	0.95	572
	2	3532.31 (p=.0,df=58)	.051	0.14	0.96	453.90
	6	**1492.40 (p=.0,df=49)**	**.022**	**0.053**	**0.99**	**185.92**
Female	1	14274 (p=.0,df=88)	.054	0.086	0.95	1688.92
	2	7200.50 (p=.0,df=81)	.040	0.11	0.98	952.90
	7	**2030.97 (p=.0,df=67)**	**.017**	**0.042**	**1.00**	**294.74**
White	1	10868.86 (p=.0,df=88)	.055	0.12	0.93	2042.04
	2	6407.11 (p=.0,df=81)	.043	0.11	0.97	943.22
	7	**1841.71 (p=.0,df=67)**	**.019**	**0.048**	**1.00**	**298.92**
Black	1	7549.13 (p=.0,df=88)	.055	0.14	0.95	980.01
	2	4666.80 (p=.0,df=81)	.037	0.11	0.98	508.22
	7	**1317.03 (p=.0,df=67)**	**.011**	**0.051**	**1.00**	**196.27**

RMSEA: root mean square error of approximation, SRMR: standardized root mean residual, CFI: comparative fit index, AIC: Akaike's Information Criterion

Table 31: Predictive Validity of Comorbidity Index in Healthcare related Behaviors (male)

Outcome variable: Medication adherence[a]	Goodness of Fit for overall model				
	Hosemer & Lemeshow[c]	LR[d]	Deviance[e]	$R^{2,d}$	AIC[e]
Uni-dimensional					
Simple count scores	2.93, df=8, p=.94	152.44	1209.87	0.183	1239.87
Empirically driven weighted scores	4.85, df=8, p=.77	151.70	1210.60	0.183	1240.60
2-dimensional: Physical					
Simple count scores	3.29, df=8, p=.94	153.11	1209.20	0.184	1239.20
Originally assigned weighted scores	5.14, df=8, p=.74	153.95	1208.36	0.185	1238.36
Empirically driven weighted scores	6.43, df=8, p=.60	150.90	1211.41	0.181	1241.41
2-dimensional: Mental					
Simple count scores	7.30, df=8, p=.50	154.55	1207.76	0.185	1237.76
Originally assigned weighted scores	4.77, df=8, p=.78	151.38	1210.93	0.182	1240.93
Empirically driven weighted scores	4.57, df=8, p=.80	156.54	1205.77	0.187	1235.77
6-dimensional					
Simple count scores	2.46, df=8, p=.96	177.58	1184.73	0.211	1232.73
Factor loading based weighted scores	4.36, df=8, p=.82	177.83	1184.48	0.211	1232.48

Outcome variable: Physician treatment adherence[b]	Goodness of Fit for overall model				
	LR[d]	Deviance[e]	Pseudo-$R^{2,d}$	AIC[e]	BIC[e]
Uni-dimensional					
Simple count scores	240.45	3557.51	0.23	3587.51	3662.45
Empirically driven weighted scores	240.51	3557.45	0.23	3587.45	3662.38
2-dimensional: Physical					
Simple count scores	240.56	3557.40	0.23	3587.40	3662.34
Originally assigned weighted scores	240.53	3557.43	0.23	3587.43	3662.36
Empirically driven weighted scores	240.72	3557.24	0.23	3587.24	3662.18
2-dimensional: Mental					
Simple count scores	240.32	3557.64	0.23	3587.64	3662.58
Originally assigned weighted scores	240.33	3557.63	0.23	3587.63	3662.57
Empirically driven weighted scores	240.33	3557.63	0.23	3587.63	3662.56
6-dimensional					
Simple count scores	**270.63**	**3554.33**	**0.26**	**3602.33**	**3722.23**
Factor loading based weighted scores	**270.75**	**3554.21**	**0.26**	**3602.21**	**3722.11**

a: analysis based on logistic regression, b: analysis based standard Poisson regression,
c: a finding of non-significance corresponds to the researcher concluding the model adequately fits the data,
d: larger values indicate better model fit, e: smaller values indicates better model fit
LR: likelihood ratio for goodness of fit

Table 32: Predictive Validity of Comorbidity Index in Healthcare Utilization (male)

Outcome variable: Hospitalization[a]	**Goodness of Fit for overall model**				
	LR[d]	**Deviance[e]**	**Adjusted $R^{2,d}$**	**AIC[e]**	**BIC[e]**
Uni-dimensional					
Simple count scores	167.29	1492.14	0.182	1568.14	1757.98
Empirically driven weighted scores	165.04	1494.38	0.180	1570.38	1760.22
2-dimensional: Physical					
Simple count scores	167.91	1491.52	0.182	1567.52	1757.35
Originally assigned weighted scores	169.95	1489.47	0.184	1565.47	1755.31
Empirically driven weighted scores	166.49	1492.93	0.181	1568.93	1758.77
2-dimensional: Mental					
Simple count scores	163.93	1495.50	0.178	1571.50	1761.34
Originally assigned weighted scores	163.40	1496.03	0.178	1572.03	1761.87
Empirically driven weighted scores	162.66	1496.76	0.177	1572.76	1762.60
6-dimensional					
Simple count scores	**176.37**	**1483.06**	**0.191**	**1577.06**	**1811.86**
Factor loading based weighted scores	**176.06**	**1483.37**	**0.191**	**1577.37**	**1812.17**
Outcome variable: Emergency room visits[a]	**Goodness of Fit for overall model**				
	LR[d]	**Deviance[e]**	**Pseudo-$R^{2,d}$**	**AIC[e]**	**BIC[e]**
Uni-dimensional					
Simple count scores	154.20	1136.92	0.190	1212.92	1402.76
Empirically driven weighted scores	127.14	1163.99	0.158	1241.99	1436.82
2-dimensional: Physical					
Simple count scores	155.20	1135.93	0.191	1211.93	1401.76
Originally assigned weighted scores	156.79	1134.34	0.193	1212.34	1407.17
Empirically driven weighted scores	145.45	1145.67	0.180	1221.67	1411.51
2-dimensional: Mental					
Simple count scores	150.80	1140.32	0.186	1216.32	1406.16
Originally assigned weighted scores	128.24	1162.88	0.160	1240.88	1435.72
Empirically driven weighted scores	123.45	1167.68	0.154	1237.68	1412.53
6-dimensional					
Simple count scores	**158.88**	**1132.24**	**0.195**	**1228.24**	**1468.04**
Factor loading based weighted scores	**158.11**	**1133.01**	**0.194**	**1225.01**	**1454.82**
Outcome variable: Outpatient visits[a]	**Goodness of Model Fit**				
	LR[d]	**Deviance[e]**	**Pseudo-$R^{2,d}$**	**AIC[e]**	**BIC[e]**
Uni-dimensional					
Simple count scores	918.902	8527.21	0.569	8605.21	8800.04
Empirically driven weighted scores	911.89	8534.21	0.566	8612.21	8807.05
2-dimensional: Physical					
Simple count scores	912.38	8533.73	0.566	8611.73	8806.57
Originally assigned weighted scores	906.62	8539.49	0.564	8617.49	8812.32
Empirically driven weighted scores	910.62	8535.49	0.566	8613.49	8808.32

2-dimensional: Mental					
Simple count scores	910.64	8535.47	0.566	8613.47	8808.30
Originally assigned weighted scores	916.06	8530.05	0.568	8608.05	8802.89
Empirically driven weighted scores	906.68	8539.43	0.564	8617.43	8812.27
6-dimensional					
Simple count scores	**929.95**	**8516.16**	**0.573**	**8612.16**	**8851.96**
Factor loading based weighted scores	**929.18**	**8516.93**	**0.573**	**8612.93**	**8852.73**

a: analysis based on zero-inflated Poisson regression. d: larger values indicate better model fit, e: smaller values indicates better model fit. LR: likelihood ratio for goodness of fit

Table 33: Predictive Validity of Comorbidity Index in Healthcare Expenditures (male)

Outcome variable: Total costs[a]	Goodness of Fit for overall model				
	LR[d]	Deviance[e]	Pseudo-$R^{2,d}$	AIC[e]	BIC[e]
Uni-dimensional					
Simple count scores	804.32	2102.58	0.362	19.63	-5375.90
Empirically driven weighted scores	784.13	2122.08	0.353	19.64	-5356.39
2-dimensional: Physical					
Simple count scores	812.35	2094.54	0.366	19.62	-5383.94
Originally assigned weighted scores	811.40	2096.74	0.366	19.62	-5381.73
Empirically driven weighted scores	797.97	2108.46	0.360	19.63	-5370.01
2-dimensional: Mental					
Simple count scores	798.87	2107.67	0.360	19.63	-5370.81
Originally assigned weighted scores	789.76	2116.56	0.356	19.64	-5361.92
Empirically driven weighted scores	780.43	2125.59	0.352	19.65	-5352.88
6-dimensional					
Simple count scores	**834.35**	**2076.47**	**0.376**	**19.62**	**-5339.04**
Factor loading based weighted scores	**833.10**	**2077.79**	**0.375**	**19.62**	**-5337.73**
Outcome variable: Diabetes care related costs[a]	**Goodness of Fit for overall model**				
	LR[d]	**Deviance[e]**	**Pseudo-$R^{2,d}$**	**AIC[e]**	**BIC[e]**
Uni-dimensional					
Simple count scores	1368.54	2794.19	0.702	16.63	-4684.29
Empirically driven weighted scores	1366.45	2801.72	0.701	16.65	-4672.77
2-dimensional: Physical					
Simple count scores	1428.49	2749.23	0.733	16.58	-4729.25
Originally assigned weighted scores	1422.99	2759.99	0.730	16.59	-4718.49
Empirically driven weighted scores	1290.31	2864.80	0.662	16.71	-4613.67
2-dimensional: Mental					
Simple count scores	1338.45	2813.69	0.687	16.66	-4664.78
Originally assigned weighted scores	1307.76	2846.58	0.671	16.69	-4631.89
Empirically driven weighted scores	1294.07	2862.76	0.664	16.70	-4615.72
6-dimensional					
Simple count scores	**1603.95**	**2589.50**	**0.823**	**16.44**	**-4826.02**
Factor loading based weighted scores	**1598.06**	**2594.23**	**0.820**	**16.44**	**-4821.28**

a: based on general-linear regression analysis d: larger values indicate better model fit, e: smaller values indicates better model fit. LR: likelihood ratio for goodness of fit

Table 34: Predictive Validity of Comorbidity Index in Healthcare related Behaviors (female)

Outcome variable: Medication adherence[a]	Goodness of Fit for overall model				
	Hosemer & Lemeshow[c]	LR[d]	Deviance[e]	Adjusted $R^{2,d}$	AIC[e]
Uni-dimensional					
Simple count scores	11.07, df=8, p=.20	576.39	3424.82	0.237	3454.82
Empirically driven weighted scores	17.00, df=8, p=.03	575.71	3425.50	0.236	3455.50
2-dimensional: Physical					
Simple count scores	14.77, df=8, p=.06	575.85	3425.36	0.236	3455.36
Originally assigned weighted scores	12.52, df=8, p=.13	576.23	3424.98	0.237	3454.98
Empirically driven weighted scores	13.86, df=8, p=.09	576.21	3425.01	0.237	3455.01
2-dimensional: Mental					
Simple count scores	9.12, df=8, p=.33	577.93	3423.28	0.237	3453.28
Originally assigned weighted scores	8.54, df=8, p=.38	577.38	3423.83	0.237	3453.83
Empirically driven weighted scores	18.6, df=8, p=.017	575.72	3425.50	0.236	3455.50
7-dimensional					
Simple count scores	9.25, df=8, p=.32	583.98	3417.23	0.239	3469.23
Factor loading based weighted scores	10.66, df=8, p=.22	584.04	3417.18	0.239	3469.18

Outcome variable: Physician treatment adherence[b]	Goodness of Fit for overall model				
	LR[d]	Deviance[e]	Adjusted-$R^{2,d}$	AIC[e]	BIC[e]
Uni-dimensional					
Simple count scores	108.51	9784.64	0.36	9814.642	9904.85
Empirically driven weighted scores	6 111.50	9781.66	0.37	9811.662	9901.87
2-dimensional: Physical					
Simple count scores	110.01	9783.15	0.36	9813.15	9903.36
Originally assigned weighted scores	106.81	9786.35	0.36	9816.35	9906.56
Empirically driven weighted scores	109.75	9783.41	0.36	9813.41	9903.62
2-dimensional: Mental					
Simple count scores	105.46	9787.70	0.36	9817.70	9907.91
Originally assigned weighted scores	105.37	9787.79	0.36	9817.79	9908.00
Empirically driven weighted scores	106.10	9817.06	0.36	9817.06	9907.27
7-dimensional					
Simple count scores	127.54	9765.62	0.43	9817.62	9973.98
Factor loading based weighted scores	127.67	9765.49	0.43	9817.49	9973.85

a: analysis based on logistic regression, b: analysis based standard Poisson regression,
c: a finding of non-significance corresponds to the researcher concluding the model adequately fits the data,
d: larger values indicate better model fit, e: smaller values indicates better model fit
LR: likelihood ratio for goodness of fit

Table 35: Predictive Validity of Comorbidity Index in Healthcare Utilization (female)

Outcome variable: Hospitalization[a]	Goodness of Fit for overall model				
	LR[d]	Deviance[e]	Adjusted $R^{2,d}$	AIC[e]	BIC[e]
Uni-dimensional					
Simple count scores	317.78	4161.26	0.129	4235.56	4457.78
Empirically driven weighted scores	327.29	4151.75	0.133	4225.75	4448.27
2-dimensional: Physical					
Simple count scores	316.23	4162.81	0.129	4236.81	4459.33
Originally assigned weighted scores	317.06	4161.98	0.129	4235.98	4458.50
Empirically driven weighted scores	324.42	4154.62	0.132	4228.64	4451.14
2-dimensional: Mental					
Simple count scores	320.78	4158.26	0.130	4232.26	4454.78
Originally assigned weighted scores	319.13	4159.91	0.130	4233.91	4456.43
Empirically driven weighted scores	324.37	4154.67	0.132	4228.67	4451.19
6-dimensional					
Simple count scores	**343.27**	**4135.77**	**0.139**	**4231.77**	**4520.44**
Factor loading based weighted scores	**343.38**	**4135.66**	**0.139**	**4231.66**	**4520.33**
Outcome variable: Emergency room visits[a]	**Goodness of Fit for overall model**				
	LR[d]	**Deviance[e]**	**Adjusted -$R^{2,d}$**	**AIC[e]**	**BIC[e]**
Uni-dimensional					
Simple count scores	302.90	2722.07	0.151	2798.07	3026.60
Empirically driven weighted scores	309.27	2715.70	0.154	2791.70	3020.24
2-dimensional: Physical					
Simple count scores	301.74	2723.23	0.150	2799.23	3027.76
Originally assigned weighted scores	302.27	2722.70	0.150	2798.70	3027.23
Empirically driven weighted scores	304.89	2720.08	0.152	2798.08	3032.62
2-dimensional: Mental					
Simple count scores	304.97	2720.00	0.152	2796.00	3024.53
Originally assigned weighted scores	302.86	2722.11	0.151	2798.11	3026.65
Empirically driven weighted scores	307.41	2717.56	0.153	2795.56	3030.11
6-dimensional					
Simple count scores	**321.25**	**2703.72**	**0.159**	**2803.72**	**3104.42**
Factor loading based weighted scores	**321.50**	**2703.47**	**0.160**	**2803.47**	**3104.17**
Outcome variable: Outpatient visits[a]	**Goodness of Fit for overall model**				
	LR[d]	**Deviance[e]**	**Adjusted -$R^{2,d}$**	**AIC[e]**	**BIC[e]**
Uni-dimensional					
Simple count scores	2643.81	23517.50	0.583	23591.50	23814.02
Empirically driven weighted scores	2685.53	23475.79	0.589	23549.79	23772.31
2-dimensional: Physical					
Simple count scores	2616.75	23544.56	0.579	23612.56	23817.04
Originally assigned weighted scores	2611.79	23549.53	0.579	23623.53	23846.05
Empirically driven weighted scores	2559.13	23602.19	0.571	23676.19	23898.70

2-dimensional: Mental					
Simple count scores	2595.84	23565.48	0.576	23639.48	23862.00
Originally assigned weighted scores	2655.68	23505.63	0.585	23573.63	23778.11
Empirically driven weighted scores	2639.26	23522.05	0.582	23586.05	23778.50
6-dimensional					
Simple count scores	**2694.23**	**23467.09**	**0.590**	**23563.09**	**23851.76**
Factor loading based weighted scores	**2686.14**	**23475.17**	**0.589**	**23569.17**	**23851.83**

a: analysis based on zero-inflated Poisson regression
d: larger values indicate better model fit, e: smaller values indicates better model fit. LR: likelihood ratio for goodness of fit

Table 36: Predictive Validity of Comorbidity Index in Healthcare Expenditures (female)

Outcome variable: Total costs[a]	Goodness of Fit for overall model				
	LR[d]	Deviance[e]	Pseudo-$R^{2,d}$	AIC[e]	BIC[e]
Uni-dimensional					
Simple count scores	1762.48	5492.75	0.289	19.63	-18549.26
Empirically driven weighted scores	1762.49	5492.04	0.289	19.61	-18549.97
2-dimensional: Physical					
Simple count scores	1752.93	5501.60	0.287	19.62	-18540.42
Originally assigned weighted scores	1757.74	5497.46	0.288	19.63	-18544.55
Empirically driven weighted scores	1758.98	5495.68	0.288	19.61	-18546.33
2-dimensional: Mental					
Simple count scores	1757.49	5497.85	0.288	19.64	-18544.17
Originally assigned weighted scores	1772.87	5481.67	0.291	19.62	-18560.35
Empirically driven weighted scores	1759.50	5495.00	0.288	19.61	-18547.02
6-dimensional					
Simple count scores	**1819.59**	**5434.60**	**0.289**	**19.60**	**-18519.26**
Factor loading based weighted scores	**1821.15**	**5432.97**	**0.299**	**19.60**	**-18520.89**

Outcome variable: Diabetes care related costs[a]	Goodness of Fit for overall model				
	LR[d]	Deviance[e]	Pseudo-$R^{2,d}$	AIC[e]	BIC[e]
Uni-dimensional					
Simple count scores	1968.14	8046.73	0.372	16.85	-15995.28
Empirically driven weighted scores	2026.36	8012.49	0.383	16.84	-16029.53
2-dimensional: Physical					
Simple count scores	1946.07	8063.01	0.368	16.86	-15979.01
Originally assigned weighted scores	1967.14	8050.41	0.372	16.86	-15991.61
Empirically driven weighted scores	1973.67	8046.15	0.373	16.85	-15995.86
2-dimensional: Mental					
Simple count scores	1945.58	8051.57	0.368	16.86	-15990.45
Originally assigned weighted scores	1980.81	8019.57	0.375	16.85	-16022.44
Empirically driven weighted scores	2009.61	8015.72	0.373	16.84	-16026.3
6-dimensional					
Simple count scores	**2061.45**	**8005.76**	**0.390**	**16.83**	**-15948.1**
Factor loading based weighted scores	**2063.39**	**8007.04**	**0.390**	**16.83**	**-15946.82**

a: analysis based on the general linear model

d: larger values indicate better model fit, e: smaller values indicates better model fit. LR: likelihood ratio for goodness of fit

Table 37: Influence of Comorbidity Dimensions on Healthcare related Behaviors

Outcome variable: Patient medication adherence

Subgroup Independent	Female β (S.E.)	Male β (S.E.)	White β (S.E.)	Black β (S.E.)
Multi-indicator dimension				
Heart diseases[1]	-0.09 (.11)	0.12 (.17)	0.05 (.12)	-0.10 (.15)
Lung disorders[2]	0.11 (.12)	-0.31 (.15)*	0.13 (.13)	-0.16 (.18)
Rheumatic disorders[3]	0.06 (.12)	-0.46 (.26)	-0.23 (.14)	-0.10 (.19)
Neurologic disorders[4]	-0.11 (.07)*	-0.32 (.14)**	-0.09 (.08)	-0.19 (.09) *
Gastrointestinal disorders[5]	-0.02 (.16)	0.01 (.2)	0.20 (.16)	-0.09 (.24)
Liver disorders[6]	0.14 (.11)	0.37 (.2)	0.05 (.12)	0.19 (.16)
Mental disorders[7]	-0.04 (.09)	-0.18 (.19)	-0.24 (.1)**	-0.05 (.15)
Single-indicator dimension				
Spinal column disorders	0.04 (.1)	-0.24 (.18)	-0.17 (.11)	-0.02 (.15)
Thyroid disorder	0.01 (.12)	------	-0.13 (.14)	------
Vision disorders	0.02 (.12)	-0.66 (.24)**	0.03 (.13)	0.06 (.18)
Epilepsy, convulsions	-0.06 (.09)	-0.08 (.16)	-0.02 (.1)	0.02 (.13)
Anemia	-0.17 (.14)	------	------	-0.05 (.18)

Outcome variable : Physician treatment adherence

Subgroup Independent	Female β (S.E.)	Male β (S.E.)	White β (S.E.)	Black β (S.E.)
Multi-indicator dimension				
Heart diseases[1]	-0.03 (.02)	0.03 (.03)	-0.01 (.02)	0.01 (.03)
Lung disorders[2]	0.03 (.02)	-0.02 (.02)	0.04 (.02)*	-0.06 (.04)
Rheumatic disorders[3]	0.03 (.02)	-0.07 (.04)*	0.05 (.02)*	0.01 (.04)
Neurologic disorders[4]	-0.01 (.01)	-0.04 (.03)*	-0.03 (.01)*	-0.01 (.02)
Gastrointestinal disorders[5]	0.05 (.03)	0.03 (.03)	0.03 (.03)	0.01 (.04)
Liver disorders[6]	0.06 (.02)**	0.00 (.03)	0.07 (.02)***	0.10 (.03)**
Mental disorders[7]	0.00 (.02)	0.00 (.03)	0.00 (.02)	0.03 (.03)
Single-indicator dimension				
Spinal column disorders	0.02 (.02)	0.01 (.03)	-0.01 (.02)	-0.04 (.03)
Thyroid disorder	0.08 (.02)***	------	0.05 (.02)*	------
Vision disorders	0.07 (.02)***	0.00 (.03)	0.02 (.02)	0.06 (.03)*
Epilepsy, convulsions	0.00 (.02)	0.03 (.03)	0.02 (.02)	0.00 (.03)
Anemia	-0.05 (.03) *	------	------	-0.02 (.04)

1: measured by arrhythmias, heart failure, and ischemic heart disease, 2: measured by obstructive pulmonary disease and asthma, 3: measured by rheumatoid arthritis and rheumatic disorders, and osteoarthritis and non-traumatic joint disorders, 4: measured by degenerative neurologic disorders and headaches, 5: measured by esophageal disorders, and gastric and duodenal ulcer, 6: measured by hepatitis, and biliary and liver disorders, 7: measured by anxiety and depression, and affective disorders, schizophrenia, other psychoses

*: p<.05, **p<.01, ***p<.001

Table 38: Influence of Comorbidity Dimensions on Healthcare Utilization

Outcome variable: Number of Hospitalization				
Subgroup **Independent variable**	**Female** β (S.E.)	**Male** β (S.E.)	**White** β (S.E.)	**Black** β (S.E.)
Multi-indicator dimension				
Heart diseases[1]	0.16 (.11)	0.37 (.14)***	0.19 (.09)**	0.22 (.13)*
Lung disorders[2]	0.22 (.1)*	0.10 (.12)	0.29 (.11)***	0.30 (.13)*
Rheumatic disorders[3]	-0.16 (.12)	-0.02 (.23)	-0.09 (.14)	-0.12 (.18)
Neurologic disorders[4]	-0.03 (.07)	0.15 (.13)	0.02 (.07)	0.02 (.09)
Gastrointestinal disorders[5]	-0.09 (.14)	0.12 (.17)	-0.16 (.14)	-0.21 (.22)
Liver disorders[6]	-0.03 (.11)	0.29 (.19)	-0.03 (.11)	-0.13 (.15)
Mental disorders[7]	0.00 (.09)	-0.10 (.18)	0.17 (.09)*	-0.06 (.16)
Single-indicator dimension				
Spinal column disorders	0.03 (.09)	0.11 (.17)	-0.01 (.1)	0.14 (.15)
Thyroid disorder	0.11 (.11)	------	0.18 (.13)	------
Vision disorders	-0.19 (.12)	-0.11 (.2)	-0.06 (.13)	-0.04 (.2)
Epilepsy, convulsions	0.09 (.09)	-0.13 (.17)	0.16 (.11)	0.14 (.13)
Anemia	0.43 (.14)**	------	------	0.02 (.16)
Outcome variable: Number of Emergency room visit				
Subgroup **Independent variable**	**Female** β (S.E.)	**Male** β (S.E.)	**White** β (S.E.)	**Black** β (S.E.)
Multi-indicator dimension				
Heart diseases[1]	0.02 (.14)	0.27 (.16)	0.10 (.12)	0.18 (.14)
Lung disorders[2]	0.29 (.13)**	0.20 (.14)	0.36 (.13)**	0.28 (.16)*
Rheumatic disorders[3]	-0.12 (.16)	-0.08 (.29)	-0.02 (.17)	0.03 (.25)
Neurologic disorders[4]	0.06 (.09)	0.22 (.15)	0.08 (.09)	0.00 (.13)
Gastrointestinal disorders[5]	-0.16 (.19)	0.08 (.19)	-0.23 (.18)	-0.19 (.26)
Liver disorders[6]	-0.01 (.14)	0.24 (.21)	0.05 (.13)	-0.15 (.21)
Mental disorders[7]	-0.09 (.12)	0.02 (.22)	0.20 (.13)	-0.23 (.18)
Single-indicator dimension				
Spinal column disorders	-0.08 (.12)	0.10 (.2)	-0.07 (.12)	-0.06 (.17)
Thyroid disorder	0.19 (.16)	------	0.17 (.15)	------
Vision disorders	-0.33 (.17)	0.10 (.22)	0.00 (.16)	-0.10 (.26)
Epilepsy, convulsions	0.18 (.13)	-0.15 (.19)	0.21 (.14)	0.26 (.15)*
Anemia	0.36 (.18)*	------	------	0.07 (.22)
Outcome variable: Number of Outpatient visit				
Subgroup Independent variable	**Female** β (S.E.)	**Male** β (S.E.)	**White** β (S.E.)	**Black** β (S.E.)
Multi-indicator dimension				
Heart diseases[1]	0.12 (.04)**	0.12 (.05)**	0.10 (.04)**	0.16 (.04)***
Lung disorders[2]	0.14 (.03)***	0.05 (.04)	0.14 (.04)***	0.16 (.05)***
Rheumatic disorders[3]	0.08 (.04)*	0.01 (.08)	0.08 (.05)*	0.05 (.05)
Neurologic disorders[4]	0.01 (.02)	0.05 (.05)	0.04 (.03)	-0.02 (.02)
Gastrointestinal disorders[5]	0.04 (.04)	0.03 (.06)	-0.04 (.04)	0.11 (.06)*
Liver disorders[6]	0.03 (.03)	0.04 (.06)	0.03 (.04)	0.09 (.05)*

Mental disorders[7]	0.21 (.03)***	0.22 (.07)***	0.26 (.04)***	0.28 (.05)***
Single-indicator dimension				
Spinal column disorders	0.06 (.03)*	0.05 (.06)	-0.01 (.03)	0.05 (.05)
Thyroid disorder	-0.01 (.03)	------	0.01 (.04)	------
Vision disorders	0.07 (.04)*	0.11 (.07)	0.06 (.05)	0.08 (.05)
Epilepsy, convulsions	0.05 (.03)*	0.12 (.06)*	0.05 (.03)	0.15 (.04)***
Anemia	0.08 (.05)	------	------	0.07 (.05)

1: measured by arrhythmias, heart failure, and ischemic heart disease, 2: measured by obstructive pulmonary disease and asthma, 3: measured by rheumatoid arthritis and rheumatic disorders, and osteoarthritis and non-traumatic joint disorders, 4: measured by degenerative neurologic disorders and headaches, 5: measured by esophageal disorders, and gastric and duodenal ulcer, 6: measured by hepatitis, and biliary and liver disorders, 7: measured by anxiety and depression, and affective disorders, schizophrenia, other psychoses

*: p<.05, **p<.01, ***p<.001

Table 39: Influence of Comorbidity Dimensions on Healthcare Expenditures

Outcome variable: Total costs

Subgroup Independent variable	Female β (S.E.)	Male β (S.E.)	White β (S.E.)	Black β (S.E.)
Multi-indicator dimension				
Heart diseases[1]	1.03 (.1)	1.43 (.23)**	1.19 (.1)*	1.34 (.17)**
Lung disorders[2]	1.21 (.13)*	1.11 (.16)	1.11 (.11)	1.64 (.25)***
Rheumatic disorders[3]	1.06 (.12)	1.12 (.29)	1.02 (.11)	1.10 (.18)
Neurologic disorders[4]	1.04 (.06)	1.29 (.16)*	1.11 (.06)*	0.97 (.07)
Gastrointestinal disorders[5]	1.00 (.14)	1.05 (.2)	0.84 (.1)	1.09 (.23)
Liver disorders[6]	0.84 (.08)	0.94 (.17)	1.02 (.09)	0.85 (.12)
Mental disorders[7]	1.18 (.1)*	1.08 (.2)	1.24 (.1)**	1.28 (.17)*
Single-indicator dimension				
Spinal column disorders	1.10 (.09)	0.94 (.16)	0.94 (.08)	1.11 (.14)
Thyroid disorder	1.04 (.11)	------	1.21 (.13)*	------
Vision disorders	0.97 (.1)	1.10 (.22)	0.99 (.09)	1.24 (.19)
Epilepsy, convulsions	1.04 (.09)	0.96 (.15)	1.10 (.08)	1.20 (.14)
Anemia	1.39 (.17)	------	------	0.97 (.15)

Outcome variable: Diabetes care related costs

Subgroup Independent variable	Female β (S.E.)	Male β (S.E.)	White β (S.E.)	Black β (S.E.)
Multi-indicator dimension				
Heart diseases[1]	1.21 (.25)	1.90 (.48)**	1.20 (.25)	2.11 (.59)***
Lung disorders[2]	1.44 (.32)*	1.68 (.37)**	1.34 (.29)	1.69 (.58)
Rheumatic disorders[3]	1.20 (.28)	1.02 (.4)	1.57 (.37)*	1.48 (.53)
Neurologic disorders[4]	1.01 (.12)	1.85 (.35)***	1.12 (.15)	1.04 (.18)
Gastrointestinal disorders[5]	0.91 (.26)	1.13 (.32)	0.67 (.17)	1.15 (.55)
Liver disorders[6]	1.06 (.23)	0.86 (.23)	1.12 (.23)	0.74 (.23)
Mental disorders[7]	1.25 (.21)	1.28 (.34)	1.28 (.23)	1.34 (.39)
Single-indicator dimension				
Spinal column disorders	0.97 (.17)	1.50 (.4)	1.06 (.2)	0.90 (.25)
Thyroid disorder	0.89 (.21)	------	1.21 (.29)	------
Vision disorders	0.81 (.18)	1.96 (.58)*	1.37 (.29)	1.12 (.39)
Epilepsy, convulsions	0.96 (.17)	0.61 (.13)**	1.10 (.19)	1.24 (.31)
Anemia	1.24 (.33)	------	------	1.75 (.6)

1: measured by arrhythmias, heart failure, and ischemic heart disease, 2: measured by obstructive pulmonary disease and asthma, 3: measured by rheumatoid arthritis and rheumatic disorders, and osteoarthritis and non-traumatic joint disorders, 4: measured by degenerative neurologic disorders and headaches, 5: measured by esophageal disorders, and gastric and duodenal ulcer, 6: measured by hepatitis, and biliary and liver disorders, 7: measured by anxiety and depression, and affective disorders, schizophrenia, other psychoses

*: p<.05, **p<.01, ***p<.001

Chapter
7. Overall Dissertation Conclusion

This study had three objectives; the primary objective of this study was to evaluate and compare the predictive performances of four comorbidity indexes- the CCI, EI, CDS and HRQL-CI, in healthcare behaviors, utilization and expenditures. We demonstrated comparative predictive performances of these indexes for a given healthcare outcome and differential performances of individual index across different healthcare outcomes. Our findings supported previous research suggestion that the choice of comorbidity index should concern the context of healthcare outcome of interest because the predictive ability of comorbidity index varied in the outcome of interest. In the other words, it is less psychometric sound to have one comorbidity index used for all healthcare outcomes; however, most research today chose comorbidity index based on the convenience of data source for measuring comorbidities or simply on the most convenient method of measurement, rather than considering relative predictive performances of alternative comorbidity indices for a given outcome of interest. In this regard, our findings could serve as empirical evidence for the selection of existing comorbidity indexes specifically for Medicaid receipts with diabetes. Our results revealed potentially most valid comorbidity index for a given healthcare outcome and the magnitude and direction of the impact of comorbid burden on a given healthcare outcome. For physician treatment adherence behavior as outcome data, the CDS could be most appropriate comorbidity measurement for risk adjustment. According to CDS based comorbidity scores, comorbidities had a positive impact on physician treatment compliance behavior. To analyze medication adherence outcome, the CDS and HRQL-CI mental aspect index could be relatively valid risk adjustment tool for overall comorbidities and mental aspect of comorbid burden, respectively. Our results further demonstrated that mental illness burden as measured by HRQL-CI mental aspect

of index had a negative effect on medication adherence, while overall illness burden measured by the CDS may enhance patient to adhere OAD medication. When healthcare utilization and expenditures as outcomes of interest, diagnosis-driven comorbidity indexes (i.e., CCI and EI) had better predictive performance than pharmacy claims based comorbidity measures (i.e., CDS). And, as comorbidtiy burden increases, medical consumption and spending increases.

Secondly, we demonstrated the performances of comorbidity index in discriminating patients varying in the demographics, healthcare behaviors, utilization and expenditures. Our findings suggested potentially most valid risk assessment tool to differentiate patients varying in these characteristics. Our findings suggested that the CDS comorbidity scores could be used to identify disadvantaged demographic populations in Medicaid setting, such as elderly and racial minority, and to differentiate patients with different physician treatment and medication adherence behaviors. Also, since diagnosis-derived comorbidity indexes (i.e., EI) provided better discrimination in healthcare utilization and expenditures outcome data than pharmacy claims based comorbidity index, healthcare policymakers could use such an index to differentiate patients with different levels of medical demand and consumption for the purpose of resource allocation.

Finally, we evaluated the dimensionality of comorbidity candidates from the HRQL-CI and compared the model fit and predictive performances among three comorbidity structures: uni-dimensional structure where all comorbidity candidates were presumed to be indicators of a single, unitary propensity to experience comorbidities; two-dimensional model where two dimensions were inspired by the clinical concept that the impacts of physical and mental illness burden on health outcomes are differential; multi-dimensional model where comorbidity dimensions were formed based on the correlation among comorbidity candidates with clinical judgments. Our results demonstrated better model fit and predictive performances of multi-dimensional model and differential impacts of individual comorbidity dimensions on healthcare outcomes. These findings implied that comorbidity scores which accounts for the characteristics of comorbidities, rather than a single summative comorbidity score, has better predictive

performance and provides insightful information about the differential influences of different types of comorbidities, which could serve as empirical evidence for further designing comorbidity management programs.

The strengths and weaknesses of this dissertation should be kept in mind when interpreting our results. The present research targeted a spectrum of critical healthcare outcomes, including healthcare behaviors, utilization and expenditures to demonstrate relative performances of individual comorbidity index across different healthcare outcomes. Also, since we incorporated several commonly used comorbidity indexes, including both diagnosis-and pharmacy claims-based measures, we were able to identify and suggest potentially most valid comorbidity index for a given healthcare outcome as well as reveal potential direction and magnitude of comorbidity impact. Moreover, we carried out the novel approaches to study the patterns of comorbidities and further to organize comorbidity candidates into meaningful comorbidity dimensions as well as to reveal potential impacts of individual comorbidity dimensions for a given healthcare outcome. These findings had critical implications for further improving comorbidity measurement and for designing comorbidity management programs.

Nevertheless, several potential study weaknesses were notable. First, the use of a claims database does have some limitations. The claims database only captures information that has been submitted for reimbursement. Also, correct categorization of insurance database information depends on correct coding by clinicians and other medical staff. Moreover, coding each ICD-9-CM claims-based measurement, there exists the possibly that ruled out diagnoses that were assigned for billing purposes were misclassified as existing comorbidities.[76] Second, data on comorbidities were limited to conditions coded on medical claims within the time frame studied. Also, comorbid candidates examined in this study were prespecified based on the diagnoses from existing comorbidity measures (e.g., CCI) and therefore, those disease diagnoses may not represent the most prevalent comorbidities in Medicaid receipts with diabetes. Fourth, a caution should be made when generalizing our results beyond the study population of continuously enrolled type 2 diabetes patients 18 to 64 years from Medicaid setting. Also, one should note

that our sample was predominantly female and White. Moreover, since we included type 2 diabetes with OAD treatment and further excluded those combing OAD with insulin therapy, our findings should only be generalizable to type 2 diabetes on OAD treatment alone. However, we were aware that those on insulin therapy tend to have poor control or worse prognosis in their diabetes disease and combine with more severe or complex health complications. In this regard, the pattern of comorbidities in type 2 diabetes requiring insulin therapy may be different from that in those with OAD treatment alone.

There are several potential future research directions. First, research has shown that estimated prevalence and pattern of comorbid illnesses in a given population were inconsistently across various data sources (e.g., medical records, claims and patient self-reported data), so none of which represents a true gold standard [404]. Such a challenge in measuring comorbid illnesses resulted that the performances of comorbidity indexes varied in the types of data sources [404]. Therefore, further research needs to validate our findings in other types of data sources for Medicaid diabetes or by combing different types of data sources. Second, because our findings showed that the performances of comorbidity index varied in the outcome of interest, research needs consistently to validate existing comorbidity indexes for a given outcome of interest, disease population and healthcare setting. Third, to our knowledge, the present study was the first research to apply confirmatory factor analysis for studying the organization of comorbidity candidates and we demonstrated improved predictive performance of comorbidity index when accounting for dimensionality of comorbidity. Our findings could serve as preliminary evidence supporting that comorbid burden was better represented by multi-dimensional, rather than uni-dimensional structure where all comorbidity candidates are presumes to be indicators of a single, unitary propensity to experience comorbidities. Also, such a uni-dimensional comorbidity structure only can be used to assess the impact of overall comorbid burden. Our proposed multi-dimensional model could be validated and refined further for improving predictive performance of comorbidity scores. Fourth, our findings that were based on patients treated with OAD alone may not be generalizable to those combing OAD with insulin

therapy. We acknowledged that type 2 diabetes patients who need insulin therapy tend to have poor diabetes disease prognosis with severe or complicated health complications so the pattern or prevalence of comorbid illnesses could be different between type 2 diabetes patients treated by OAD alone and those requiring insulin therapy. Further research should assess the difference in the pattern of comorbidities between type 2 diabetes with and without insulin therapy. If such a difference exists, the analysis regarding the impact of comorbidities should be conducted in types 2 diabetes with OAD treatment alone and those on insulin therapies separately. Lastly, instead of using comorbidity candidates from existing comorbidity index, further research should identify most prevalent or influential comorbid conditions, which are specific to a given healthcare outcome in the study population of interest, and then investigate the impact of comorbid burden on healthcare outcomes.

As acknowledged, diabetes patients in Medicaid setting were older or disable with severe and complicated comorbid complications, which caused these patients to be a costly population with high levels of healthcare use in healthcare system. Understanding and managing comorbidities provides potential promises to improve healthcare outcomes and to reduce medical consumption and spending in this population. In this regard, our findings have several implications for diabetes care in the Medicaid setting. First, in the research perspective, a valid comorbidity index for a given healthcare outcome is an essential assessment tool for assessing and controlling for the effect of comorbid burden. Our results suggest potentially most valid comorbidity index specific for a given healthcare outcome in Medicaid diabetes patients. Second, in the clinical perspective, a valid and practical comorbidity index is important for healthcare providers to predict patient's diabetes disease prognosis, healthcare behaviors and outcomes. Our findings demonstrated that mental comorbid burden had a negative impact on patient OAD adherence behavior. This implies that healthcare providers need to pay more attention on diabetes patients with mental illnesses regarding their OAD taking behavior. Regarding diabetes management, we found that the CDS comorbidity scores were most valid risk assessment to differentiate patients varying in physician's diabetes care guideline

adherence as well as their OAD adherence behaviors. This implies that patients with different quality of care or medication adherence could be differentiated using the CDS comorbidity scores and further interventions for improving diabetes management could be delivered to patients with poor diabetes management properly. Third, from policymaker's prospective, our findings supported that comorbid illnesses were positively associated with healthcare use and spending in this costly Medicaid diabetes population. In this regard, assessing co-existing medical conditions among these patients is a fundamental approach to identify patients at risk of high medical consumption and spending due to their illness burden. Comorbidity index scores that reflect severity level of illness burden could be used to differentiate patients varying in medical needs and then medical resource could be delivered properly to those with high healthcare demand. Moreover, when assessing the effect of policy intervention on healthcare utilization and costs, controlling for the effect of comorbid burden is essentially required. Because our findings showed that comorbid illnesses had significant impact on healthcare utilization and costs, without adjusting for the effect of comorbidities, the relationship between policy interventions on these healthcare outcomes could be confounded and estimated effect of policy intervention would be less valid.

In conclusion, while more work is warranted to evaluate these findings can be supported in other circumstances (e.g., disease population, healthcare setting) theses results are, nevertheless, important to healthcare service researchers in the selection and use of existing comorbidity indexes

Appendices

Appendix 1: Prescription Drug in RxRisk Algorithm

RxRisk Class	Representative Drug Class(es)
Acne, pediatric	Anti-acne peroxides, anti-acne tretinoin ,retinoids, topical macrolides,
Allergic rhinitis, pediatric	Anti-inflammatory glucocorticoi,
Amino acid disorder, pediatric	Amino acids,
Anxiety and tension, adult	**Salicylate combinations, barbiturates, benzodiazepines, meprobamate, miscellaneous hypnotics, paraldehyde,**
Anxiety and tension, pediatric	Anticholinergics, benzodiazepines,
Asthma, adult	**Anti-inflammatory glucocorticoids, isoproterenol, bronchodilators, cromolyn, xanthenes**
Asthma, pediatric	Anti-inflammatory glucocorticoids, bronchodilators, cromolyn, xanthenes
Attention deficit disorder, pediatric	Anorexics/analeptics
Bipolar disorder, adult and pediatric	Lithium
Cardiac disease, adult	**ClassI a antiarrhythmic, ClassI c antiarrhythmics. Class III antiarrhythmic, procainamide, disopyramide, quinidine, vasodilator nitrates, diuretic loops**
Cardiac disease, pediatric	Beta adrenergic blockers, ClassI a antiarrhythmic, ClassI c antiarrhythmics, ClassI II antiarrhythmic, digital isglycosides, dipyridamole, procainamide, vasodilator nitrates, calcium channel blockers, diuretic loop
Central line supplies, pediatric	Fibrinolysin antagonists, heparin
Congenital adrenal hypoplasia, pediatric	Anti-inflammatory glucocorticoids
Coronary/peripheral vascular disease, adult	**Antiplatelet, oral anticoagulants, trental**
Cystic fibrosis, adult	**Anti-inflammatory glucocorticoids, enzymes**
Cystic fibrosis, pediatric	Aminoglycosides, quinolones, antibiotic urinary tract anti-infectiveagents, mucolytics
Depression, adult	**Monoamine oxidase inhibitors, phenothiazine combinations,tricyclic anti-depressants, SSRIs**

Depression, pediatric	Monoamine oxidase inhibitors, tricyclic antidepressants
Diabetes, adult	**Biguanides, insulins, sulfonylureas**
Diabetes, pediatric	Insulin
Eczema, pediatric	Anti-inflammatory glucocorticoids, antipsoriasis combinations, topical steroids
Epilepsy, adult	**Anti-convulsants**
Epilepsy, pediatric	Anticonvulsant barbiturate +cogenerators, hydantoins
ESRD, adult	**Marrow stimulants, human erythropoietin**
Gastric acid disorder, adult	**Histamine H2b lockers, prostaglandins, proton pump inhibitor**
Gastric acid disorder, pediatric	Histamine H2b lockers, proton pump inhibitor
Gout, adult	**Colchicine, uric acid inhibitors**
Growth hormone deficiency, pediatric	Human growth hormone
Heart disease/hypertension, adult	**Beta adrenergic blockers, dopamine, calcium channel blockers**
Hemophilia, pediatric	Hemostatics
HIV, adult and pediatric	Miscellaneous anti-protozoal, antivirals, pentamidine
Hyperlipidemai, adult and pediatric	**Antilipemic dofibrate, antilipidemic exchange resins, HMG coagulant reductase inhibitors**
Hypertension, adult	**ACE inhibitors, antihypertensive vasodilators, donidine, ganglionic blockers, guanethidine, methyldopa, rauwolfia alkaloids, alpha/beta blockers, diuretic combinations, diuretic k+ depleting agents, diuretic k+ sparing agents**
Immunodeficiency, pediatric	Immune serums
Iron overload, pediatric	Heavy metal antagonists
Irritable bowel syndrome, adult and pediatric	**Sulfonamide**

Source:[179]

Appendix 2: Thomson Medstat Description

Thomson MedStat is a division of Thomson Healthcare, which is the leading provider of decision support solutions that help organizations across the healthcare industry improve clinical and business performance.
Available at: http://www.thomson.com/solutions/healthcare/

Appendix 3: Approval for Data Access and IRB Approval

UNIVERSITY OF MICHIGAN
eResearch.umich.edu
Health Sciences and Behavioral Sciences Institutional Review Board • 540 East Liberty Street, Suite 202, Ann Arbor, MI 48104-2210 • phone (734) 936-0933 • fax (734) 998-9171 • irbhsbs@umich.edu

To: Huang-Tz Ou

From:
There are no items to display

Cc:

Rajesh	Balkrishnan
Huang-Tz	Ou
Lynn	Phaneuf

Subject: Notice of Determination of "Not Regulated" Status for [HUM00035480]

SUBMISSION INFORMATION:
Title: Predictive Performance of Comorbidity Measures in Medication Adherence, Quality of Care, Healthcare Resource Utilization, and Costs in Type 2 Diabetes
Full Study Title (if applicable):
Study eResearch ID: HUM00035480
Date of this Notification from IRB: 11/30/2009
Date of IRB Not Regulated Determination : 11/30/2009

IRB NOT REGULATED STATUS:

Category	Description	Sort Order
Other	It has been determined that because your data sets are de-identified, based on the provided documentation, that this project is not considered research with human subjects.	16

Richard W Redman

Richard Redman
Chair, IRB HSBS

AMENDMENT NUMBER 1
to the
Services and License Agreement

by and between

Thomson Reuters (Healthcare) Inc.
and
The Reagents of University of Michigan

When fully executed by both parties, this document will constitute the first (1st) formal Amendment to the Services and License Agreement by and between Thomson Reuters (Healthcare) Inc. ("TRH") and The Reagents of University of Michigan ("Customer"), dated effective September 28, 2009 ("Agreement"). The purpose of this Amendment is to provide expanded use of the licensed data.

Exhibit A to this Amendment describes licensed Data and the expanded permitted use of the Data.

This Amendment will be deemed fully executed and in effect as of the date of this last signature below. All other terms and conditions of the Agreement as previously amended that are not affected by this first (1st) amendment remain in full force and effect.

FOR THOMSON REUTERS (HEALTHCARE) INC	FOR THE REAGENTS OF UNIVERSITY OF MICHIGAN
By:	By:
Name: Doreen S. Waterhouse	Name: Lalit Sharma
Title: Financial Plan Mgr.	Title: IT Purchasing Mar
Date: 4/2/2010	Date: 3/31/10

Services and License Agreement
Exhibit A
Licensed Data and License Fees

Customer's Facility:
The Data described herein are licensed to Customer for access in the Customer offices located at:

The University of Michigan
428 Church Street
Ann Arbor, MI 48109-1065

Description of the Data Licensed to Customer:
Thomson Reuters (Healthcare) Inc. will provide five complete years (2003-2007) of the MarketScan Medicaid Database and three complete years (2005-2007) of the MarketScan Commercial Claims and Encounters Database.

Authorized Users for the Data:

Thomson Reuters (Healthcare) Inc. had previously provided the following authorized use of license data within the original Exhibit A to Services and License Agreement.

These data may be used by authorized faculty and staff within the "Center for Medication Use, Policy, and Economics, University of Michigan College of Pharmacy". Graduate students within the department may use the data in support of faculty-directed research and under the supervision of faculty and/or staff within the department.

Thomson Reuters (Healthcare) Inc. is now providing via this Amendment #1 additional expanded use of the licensed data as follows:

These data may be used by authorized faculty and staff within the "Center for Medication Use, Policy, and Economics, University of Michigan College of Pharmacy" at the University of Michigan.

Graduate students may ONLY use data in support of faculty-directed research and under the supervision of faculty and/or staff within department.

Ph.D. students are not permitted to use the MarketScan Data licensed under this agreement for dissertation research with the exception of the four students listed below. Ph.D. students may apply to use the MarketScan Dissertation Database for their dissertation research.

The four University of Michigan doctoral students listed below are authorized to use the MarketScan Medicaid Database in support of the named dissertation studies below through August 31, 2010 or when they have graduated from the university whichever date is soonest.

Any use of these data by students after graduation must be covered under a MarketScan Data Rider agreement signed by an authorized representative of the University of Michigan.

List of students and dissertation research:

Huang Tz-Ou: *PREDICTIVE PERFORMANCE OF COMORBIDITY MEASURES IN MEDICATION ADHERENCE, QUALITY OF CARE, HEALTHCARE RESOURCE UTILIZATION, AND COSTS IN TYPE 2 DIABETES*

Meg Kong: *RACIAL DIFFERENCES IN MEDICATION ADHERENCE AND ASSOCIATED OUTCOMES IN A HIV-INFECTED MEDICAID POPULATION WITH POSTPARTUM DEPRESSION*

Chung-Hsuen Wu: *THE COMBINED EFFECTS OF RACE AND COMORBIDITY ON MEDICATION USE RELATED OUTCOMES IN MEDICAID ENROLLED MAJOR DEPRESSIVE DISORDER PATIENTS*

Jun Wu: *STATIN MEDICATION USE BEHAVIORS IN TYPE 2 DIABETES PATIENTS PRESENTING COMORBID HYPERLIPIDEMIA IN MEDICAID POPULATION*

Appendix 4: Selected Oral Anti-Diabetic Medications

NDC codes	Medication NDC codes			
Metformin	00087606005	00087606010	51129415501	11532002102
	00087607005	00087607010	51129415502	11532002201
	00087607111	00087607112	54868550000	54868550001
	64764015514	64764015565	64764015560	64764015518
	64764015814	64764015865	64764015860	64764015818
	00173316418	00173316461	53873316302	53873316301
	53873316300	53873316303	00007316318	00007316361
	00007316320	00007316418	00007316420	00007316461
	00007316718	00007316720	00007316761	00007316820
	00007316818	00007316861	00173316318	00173316361
	00173316718	00173316761	00173316818	00173316861
	30256316300	30256316400	30256316700	30256316800
	51129305801	51129305802	51129305901	51129305902
	53873316400	53873316401	53873316402	53873316700
	53873316701	53873316702	53873316800	53873316801
	53873316802	54868515700	54868515701	59742316300
	59742316301	59742316302	59742316304	59742316400
	59742316401	59742316402	59742316404	59742316700
	59742316701	59742316702	59742316704	59742316800
	59742316801	59742316802	59742316804	51129411301
Sulfonylureas	00009007002	00009010011	00009014101	00009017105
	00009034101	00009035201	00009344901	00009344903
	00039005110	00039005210	00039005250	00039005270
	00039005305	00039022110	00039022210	00039022310
	00047046324	00047046330	00049155066	00049155073
	00049156066	00049156073	00049162030	00049411066
	00049411073	00049412066	00093936401	00049412073
	00093936405	00069393066	00093936410	00069394066
	00093943301	00078035205	00093943305	00087606313
	00093947753	00087607211	00169008181	00087607311
	00169008281	00087607411	00169008481	00093104801
	00172224560	00093104901	00172297860	00093803501
	00172297960	00093803505	00172298060	00093803601
	00172364960	00093834201	00172364970	00093834301
	00172365060	00093834310	00172365070	00093834401
	00093834405	00093834410	00172433060	00781505201
	00781145601	52544046010	59762372603	00781505201
	00172433160	00781145701	52544046101	59762372704
	00172443260	00781145705	52544046105	59762372706
	00182199501	00781145710	52544046110	59762372707
	00182264701	00781505001	52544055901	59762378201
	00185021301	00781505101	52544055905	59762378203
	00185021501	00781505201	52544056001	97623783010
	00185022101	00904507780	53489046701	59762378302
	00228271811	00904792580	53700506070	60951071170
	00247144330	38245036410	55370050608	60951071185

	00378021001 38245036420 55953003540 62037067401 00185022105 00904792440 53489046901 59930159201 00228265711 00904792460 55370014607 59930162201 00228265750 00904792480 55370014707 59930163901 00228271511 00904792540 55370014708 59930163903 00378021010 38245036450 55953003570 62037067501 00378021501 38245038110 55953003640 62037067601 00378023401 38245038120 55953034240 62269029129 00378024001 38245038150 55953034340 62269029224 00378024401 38245043310 55953034370 62269029229 00378055101 38245043350 55953034440 62939323100 00378110501 38245047749 55953034470 00378110505 49884045201 55953034480 00378111001 49884073601 57664039788 00378111005 50111037201 59762372501 00378111301 50111037301 00781145310 00378112501 50111037303 00378114201 51285059902 00536346501 51285059904 00536346510 52544046001 00536466805 52544046005 005364739 00591245501 00536564201 00591245505 00536564301 00591271301 00536569701 00591271305 00536569801 00591277501 00536570201 00603283628 00536570205 00603375621 00536570301 00603376321 00536575101 00536575201 00603612121 00555038502 00662411066 00555038602 00662411073 00555038702 00662412066 00591046001 00663394066 00591046005 00677154501 00591046010 00781145201 00591046101 00781145210 00591046110 00781145301
Thiazlidinediones	64764015104 64764030100 64764015105 64764045125 64764045100 64764015106 11532001100 64764030115 64764030114 11532001216 11532001300 64764030116 51129177709 64764045124 51129178206 54868434301 64764045126 66332001125 64764015118 66332001201 66332001309 000293158 61 00029315918 00029316001 05112916220 05974231592 05974231609 05112916218 05974231581 00007315113 00007315213 00173315200 00173315213 00173315265 00173315313 00173315365 00173315113 00173315165 00007315213 00007315265 00007315266 00007314913 00007314965 00007314966 00007314813 00007314865 00007314866 00173314813 00173314865 00173314913 00173314965 54868537900 49990935030 00029315825 00029315838 00029315813 00029315818 00029315820 00029315822 00029315866 00029315938 00029315913 00029315918 00029315920 00029315922 00029315966 00029315925 00029316038

NDC: National drug code

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